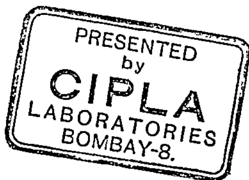
ACUTE PULMONARY EDEMA



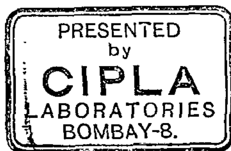
Mark D. Altschule is also author of
BODILY PHYSIOLOGY IN
MENTAL AND EMOTIONAL DISORDERS

Modern Medical Monographs **10**

ACUTE PULMONARY EDEMA

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Contents

Introduction

THIS MONOGRAPH was written for students of medicine, at school or in practice. Its purpose is to relate both the manifestations and the treatment of acute pulmonary edema to what is known about certain physiologic phenomena.

A great deal has been learned about the physiology of chronic cardiac decompensation—chiefly from studies on patients with that syndrome. This has not been possible in the case of pulmonary edema; hence observations on animals predominate in this field. However, most physicians do not keep abreast of the literature of animal experimentation; either they barely glance at such papers or else they do not read widely enough to synthesize the many small points elucidated in them. Physiologic data have therefore been emphasized here more than is customary in clinical treatises.

The clinical portions of this work contain no bibliographic references; clinical writers who have had adequate clinical experience should not have to "lard their lean books with the fat of others' works," to "skim the cream of other men's wits, pick the choice flowers of their tilled gardens to set out [their] own sterile plots," as Robert Burton put it. On the other hand, the authorship of the physiologic data used here is of course indicated; the bibliography therefore consists largely of references to experiments in animals.

It is not always easy to relate clinical phenomena to physiologic observations, some connections are evident and others are obscure. Speculation naturally arises in the latter event, and it *flourishes* when data are lacking. A curious situation obtains in the field of acute pulmonary edema: The prevailing clinical theory of its origin is *still* expressed *in precisely* the terms used when the concept was introduced, a hundred years ago. Most clinical speculations on physiologic data relating to the syndrome apparently aim to explain the physiology in terms of the current theory rather than to develop the theory on the basis of the physiology. Until recently, physiologic data on this subject were so scanty that established clinical concepts could not be adequately evaluated; nothing valid could be said either for or against them. In the past few years, however, enough data have

been published to provide a basis for criticism of current ideas. Nevertheless, knowledge is still insufficient to provide any simple alternative. No theory that fails to explain *all* physiologic findings is valid; no valid theory of the origin of pulmonary edema can be formulated at present.

This book will present available knowledge in the form of a logically coherent system of ideas that are consistent with what is observable As William James said, "A large acquaintance with particulars often makes us wiser than the possession of abstract formulas, however deep." In the present work some tentative explanations are offered (but not insisted on) where definite conclusions cannot be reached.

Writers of clinical treatises have often been accused of "serving a warmed over dish." This book, even though it contains no new information, aims to present new points of view concerning established concepts.

The invaluable editorial assistance of Miss Evelyn Russ is gratefully acknowledged.

M. D. A.

Athens, Vermont
September 1953

BY THE BED-SIDE, HOW MANY FALSE DIAGNOSTICS HAVE I NOT WITNESSED . . . WHAT IS THE SOURCE OF SUCH MISTAKES? I REPEAT IT, IT IS THE DEFICIENCY OF CORRECT PHYSIOLOGY.

J. N. Corvisart: *An Essay on the Organic Diseases and Lesions of the Heart and Great Vessels.*

I. Clinical Manifestations

THE EARLIEST DESCRIPTIONS of pulmonary edema—particularly in relation to heart disease—are to be found in the writings of Continental clinicians of the mid-eighteenth century. In the early nineteenth century, after the Napoleonic wars, clinical and pathological knowledge of cardiac and pulmonary diseases broadened considerably, acute pulmonary edema was subsequently recognized as a separate syndrome by Laennec, Corvisart, Testa, Kreysing, Burns, Stokes, Hope, and other great physicians of the period The disorder has held the interest of clinicians ever since then, because of its dramatic manifestations and its frequent refractoriness to treatment.

The clinical manifestations of acute pulmonary edema vary markedly. The severity of the condition ranges from the barely detectable to the fatal, in some patients changes in one direction or another may occur very quickly. The mild or early manifestations may be overlooked or misinterpreted, because the signs of interstitial edema of the lungs are less striking than those of intra-alveolar edema In addition, the signs and symptoms of the syndrome may be greatly modified or even overshadowed by those of the disease that caused the pulmonary edema Because attacks commonly occur at night, some authors prefer the term "paroxysmal nocturnal dyspnea" to others. Strictly speaking, this is a misnomer, since in some patients the attacks occur in relation to sleep rather than to time of day.

For the purpose of discussion it is useful to make arbitrary temporal subdivisions of an attack, as follows: (1) onset, (2) interstitial phase; (3) intra-alveolar phase, (4) shock, and (5) terminal phase.

1. Onset

The very beginning of an attack of pulmonary edema is usually not detected or is recognized only in retrospect. One reason for this is that many attacks occur late at night, but a more important reason is that the earliest symptoms and signs are nonspecific.

When an attack is developing, the patient may have no premonitory sensations; on the other hand, he may first notice a feeling of marked anxiety several minutes (occasionally, several hours) before dyspnea develops. The physician may sometimes misinterpret this anxiety as the cause rather than as the earliest symptom of the attack. Physical examination at such times reveals pallor, an anxious look, and increases in pulse rate and arterial pressure above the patient's normal range; the skin is usually cold and slightly sweaty. The hypertension may be *misinterpreted as evidence of a hypertensive* crisis that might have caused the attack. It is evident that these signs and symptoms are not specific for pulmonary edema; they can be established as part of the syndrome only if roentgenographic studies show typical areas of haziness close to the hilar regions of the lungs.

In some patients, insomnia is the only symptom of mild attacks of pulmonary edema. Strictly speaking, this specific complaint should not be called insomnia, since the patients who have it fall asleep normally but are awakened several hours later by feelings of anxiety or by terrifying dreams. The reason for believing that these symptoms do indeed represent mild attacks is that weeks or months later typical attacks of the syndrome begin to occur at the same time of night.

There are very few clinical studies of acute pulmonary edema in this early stage. In some instances the attack does not progress, and the symptoms subside. However, in most cases the syndrome probably develops further; in some instances the patient's feeling of impending disaster is fully justified by subsequent events.

2. *Interstitial Phase*

In this phase the nonspecific manifestations of the first phase persist, but they are masked by the development of more distressing symptoms related to respiration. These consist mainly in dyspnea, [illegible] is usually [illegible] combined [illegible] the ear- [illegible] arterial pressure either is elevated, as at the onset, or has returned to the patient's normal level. The neck veins are distended in many pa-

tients. Examination of the lungs shows striking prolongation of the expiratory phase of respiration. Wheezing, accompanied by musical rales and rhonchi, is marked in many cases but may be absent in others. Crackling rales are few and inconstant or are absent entirely.

This phase of the attack may last for many minutes or a few hours; on the other hand, the period in which the lungs remain free of detectable intra-alveolar fluid may be so brief as to be unmeasurable. The interstitial phase may proceed abruptly into the phase of alveolar transudation. Patients who suffer recurrent attacks learn to obtain relief by sitting up with their feet dangling, or by standing; some rush to a window and lean out in an attempt to "get more air." In many attacks, remission (either spontaneous or due to treatment) may occur before transudation into the alveoli becomes clinically detectable. The interstitial and intra-alveolar phases may alternate repeatedly. Shock may occasionally supervene in prolonged pulmonary edema of the interstitial type.

Laboratory studies show rises in hematocrit, erythrocyte count, and hemoglobin level; a lesser rise in plasma protein level may be noted. The circulation time is slowed, a few observations of cardiac output have revealed lowered values for blood flow through the lungs. The vital capacity is lowered markedly, and the arterial blood oxygen saturation falls to between 70 and 85 per cent. The right-auricular and peripheral venous pressures are elevated, but not necessarily above the upper limit of normal.

3. *Intra-alveolar Phase*

The severity of intra-alveolar accumulation of fluid varies markedly; in some patients there is only a little fluid, which is revealed by fine scattered rales, whereas in others bubbling sounds may be audible at a distance of several feet. The time of onset of this phase varies also; it may occur a few seconds or several hours after the first feeling of anxiety, or in some cases it may not appear at all. The accumulation of fluid in the alveoli and small airways usually aggravates dyspnea and causes coughing The amount of sputum produced ranges from a few cubic centimeters to a liter or more. Small amounts of mucus, varying quantities of blood, and considerable air are mixed with the plasma that is coughed up The color of the sputum, which depends

on the amount of hemoglobin contained, may range from a pale orange to the dense red of blood itself.

Examination of such patients shows moderate to marked cyanosis. Tachycardia is present; the arterial pressure is approximately at the patient's usual level. The neck veins are distended. Expiration is prolonged, and crackling or bubbling rales are audible over most of the chest. Wheezing, with its musical rales, may be present also. The crackling and musical rales are not necessarily uniform in distribution; they may be more numerous on one side or over one lobe.

Rectal temperatures of 101° F or even higher are common in patients who have acute pulmonary edema for many hours or a few days; this is owing to the impairment of heat dispersal that occurs in the syndrome. It should also be borne in mind that bacterial infection is favored by the increase of fluid in the lungs and the impairment of pulmonary function that are associated with the syndrome; patchy bronchopneumonias are commonly found at post-mortem examination in patients dying of or with pulmonary edema.

This phase of the attack may be followed by remission—either spontaneous or due to therapy. In many instances, however, shock develops. This too may be either spontaneous or due to the use of tourniquets, positive pressure respiration, or venesection. In a few cases the bubbling rales disappear and the patient reverts to the interstitial phase, with or without wheezing

Laboratory studies on patients in this state are few and fragmentary. The changes are similar to those described for the interstitial phase but may be more marked.

4. *Shock*

This condition is common in pulmonary edema. It may be caused by the factor responsible for the edema—myocardial infarction, for example—or may be a consequence of either the pulmonary edema or its treatment.

The development of shock is ushered in by clouding of consciousness in the patient; although hyperpnea is still evident, dyspnea is not prominent and orthopnea disappears The pulse rate increases and arterial pressure falls The veins are narrow and flat. Pallor, grayish cyanosis, and clammy sweating are marked. Examination

of the lungs shows signs similar to those of the earlier stages of the attack.

A few measurements of venous pressure have been made in patients with shock associated with pulmonary edema; values in the normal range occur with mild shock, but very low pressures are found in severe collapse.

The mortality rate is high in patients who have both pulmonary edema and shock. A few patients recover spontaneously; there is no strong evidence that available therapy predictably influences the outcome. The longer the shock persists, the poorer the prognosis.

5. Terminal Phase

Deepening of shock, development of coma, and the appearance of cardiac and respiratory arrhythmias indicate impending death.

Angina Pectoris and Acute Pulmonary Edema

Coronary arteriosclerosis is a common cause of acute pulmonary edema in adults, hence it is to be expected that attacks of both pulmonary edema and angina pectoris should occur in the same patient.

The onset of angina pectoris is easily recognized, but in many instances the patient may not become aware of an attack of pulmonary edema for some minutes; hence patients may state variously that the angina pectoris occurred before, after, or simultaneously with the onset of the dyspnea or wheezing of pulmonary edema If the factor responsible for the edema is one that causes an increase in cardiac work or a decrease in coronary blood flow, it may itself precipitate angina pectoris in various temporal relations to the pulmonary edema On the other hand, the anoxia caused by edema of the lungs may of itself produce anginal pain. In addition, any very uncomfortable symptom may distract the patient's attention from other symptoms; severe angina may overshadow mild or moderate pulmonary edema, or vice versa. Moreover, some patients cannot distinguish the feeling of oppression due to one symptom from that caused by the other. Stokes noted over a century ago that "the disease which in this country [Ireland] most often gets the name of angina pectoris might be more properly designated cardiac asthma."

Some patients give a history of angina pectoris, stating that that syndrome disappeared when attacks of acute pulmonary edema began. This was pointed out by Balfour sixty years ago: "Now and then ordinary attacks of painful angina cease, and towards the close of life the patient suffers only from fits of breathlessness." It is probable that this sequence of events merely indicates that the patient's heart disease has worsened and that angina pectoris has seemingly disappeared because the patient cannot exert himself as much as previously. It might also mean that the anginal discomfort has merely been overshadowed by the greater distress caused by the dyspnea of pulmonary edema.

At any rate, the occurrence of angina pectoris in association with pulmonary edema has no significance other than that of angina pectoris alone—that is, that the patient has an inadequate coronary blood flow.

Differential Diagnosis

It is usually not difficult to distinguish fully developed attacks of pulmonary edema or cardiac asthma from other syndromes. At the onset, before respiratory symptoms or abnormal pulmonary signs appear, the manifestations of the disorder are indistinguishable from those of an anxiety attack. However, this early stage of pulmonary edema is rarely observed in home practice, and only occasionally and by chance in the hospital. These early manifestations are of brief duration; they either pass off or progress to a more advanced stage of the syndrome.

Bronchial Asthma: The interstitial phase of pulmonary edema is the one most likely to cause difficulties in diagnosis—especially if

The dyspnea and wheezing respiration of pulmonary edema resemble those of bronchial asthma; the musical rales and rhonchi heard on examination, with few or no crackles or bubbles, apparently heighten this similarity.

The patient's age at the first attack of the bronchospastic syndrome

is important. Cardiac asthma is rare under the age of fifty except in association with such easily diagnosed conditions as severe cardiac, hepatic, or renal disease, beri-beri, certain pneumonias, hypertension, and a variety of traumatic, inflammatory, or neoplastic diseases of the brain.

On the other hand, first attacks of bronchial asthma rarely occur after the age of fifty except in patients with a long history of non-asthmatic bronchitis or of exposure to some industrial dust. In addition, a history of other allergic manifestations—such as rashes, hay fever, and so forth—or of chronic bronchitis is often obtained. Accordingly, attacks of asthma that occur prior to middle age ara automatically to be regarded as indicating bronchial asthma, unless proved otherwise.

Another diagnostic aid is the fact that bronchial asthma is commonly accompanied by eosinophilia, whereas in cardiac asthma the eosinophil count rises slightly at first but then usually falls; this decrease does not develop for several hours and may therefore be of little help in differential diagnosis.

Since a certain number of cases cannot be differentiated on the basis of history, and since findings at physical examination may be identical in bronchial and cardiac asthma, measurement of circulation time may be found helpful. This is normal or rapid in bronchial asthma and slowed in most cases of cardiac asthma. When borderline results are obtained with the test, or when the patient is so ill that the physician cannot risk waiting until the test can be performed, treatment may have to be instituted notwithstanding When the nature of an asthmatic attack cannot be determined on the basis of available information, aminophylline (page 53) should be used to avoid the dangers associated with the use of large doses of morphine in bronchial asthma or of epinephrine [illegible]

[illegible]

wi [illegible]

confused with other conditions. One disorder that may resemble acute pulmonary edema in some respects is not common in adults. This is an infectious process: capillary bronchitis, or acute bron- [illegible]

of rales in an attack of acute pulmonary edema. Although the disease is mainly found in children, its occasional occurrence in adults should be borne in mind, since if morphine is used in capillary bronchitis because of an erroneous diagnosis of acute pulmonary edema the results may be unfortunate.

Acute Pulmonary Edema and Chronic Cardiac Decompensation

There is a close relation between acute pulmonary edema and chronic cardiac decompensation in patients whose pulmonary edema is due to heart disease. This relation takes several forms. Some patients with chronic decompensation develop attacks of pulmonary edema (usually nocturnal) only when the chronic failure is severe. When the decompensation is treated, these attacks disappear.

Other patients exhibit an inverse temporal relation. Attacks of pulmonary edema may recur for several weeks, or even a few months, before the signs of chronic failure become striking. However, careful study of such patients, if made before venous engorgement, hepatomegaly, and edema appear, indicates that they actually have had some degree of chronic failure from the start. This is manifested by exertional dyspnea, moderate orthopnea, and a few basal rales; laboratory studies in such instances reveal slowed circulation time and diminution of the vital capacity. The acute attacks, which are usually nocturnal, are so dramatic that the slowly progressive chronic failure is sometimes overlooked until it becomes so severe as to require attention months later. On the other hand, when these changes occur in patients with syphilitic aortitis the signs of chronic failure often become striking and intractable merely a few days or a few weeks after the onset of the acute pulmonary edema. In patients of this type the pulmonary edema is probably precipitated by physiologic changes due to chronic failure (Part II).

A third type of temporal relation between chronic cardiac decompensation and acute pulmonary edema is exemplified in some patients with mitral stenosis or myocardial infarction in whom the acute syndrome ceases to occur when the chronic failure develops or at least becomes overt. The sequence of events in patients of this type has aroused much interest among clinicians, who usually describe

the situation as one of amelioration of left-ventricular failure *because of* failure of the right ventricle. Alternative interpretations suggest themselves, however.

The patients with mitral stenosis who no longer have attacks of pulmonary edema after peripheral signs of failure have developed actually show no physiologic evidence of failure of either ventricle during the period of attacks. The pulmonary edema is usually caused by tachycardia occurring under a mechanical condition that requires a slow cardiac rate—with long diastoles—for adequate blood flow through the lungs; this condition is created by marked narrowing of the mitral valve (page 33). On the other hand, studies made when the patient is in chronic failure (with peripheral edema, hepatomegaly, and venous engorgement) and free of pulmonary edema show that both ventricles have failed (page 34), despite further increases in pulmonary capillary pressure (a sign of left-ventricular weakness), the attacks of pulmonary edema disappear. This rather complex physiologic phenomenon is discussed in detail elsewhere (page 35) In occasional patients, acute attacks of edema of the lungs reappear when treatment is instituted for chronic cardiac decompensation.

The patients with myocardial infarction who exhibit severe pulmonary edema for a day or two after an attack, followed by subsidence of the pulmonary edema as the peripheral signs of chronic failure develop, have probably had both syndromes from the very start. It has been amply demonstrated that the body's extracellular fluid volume must be increased by a quarter or a third of its normal value before peripheral edema can be detected. The appearance of peripheral edema (and the other peripheral signs of failure) on the third or fourth day after myocardial infarction indicates that the chronic failure began several days earlier, pulmonary edema that follows myocardial infarction is often self-limited, lasting for a few hours to a few days. In patients of the type discussed here, each of the two syndromes—acute pulmonary edema and chronic cardiac decompensation—goes through its normal evolution independently, and the temporal relation may misleadingly resemble a causal relation. Certainly, judgment in clinical problems of this sort should be reserved until enough physiologic data is at hand to ensure valid interpretations.

Prognosis

The outcome of attacks of pulmonary edema is most uncertain. Although the use of modern methods of treatment has increased the likelihood of recovery from an attack, many patients still die of the syndrome. Most of the factors that determine the outcome are inherent in the disease that caused the pulmonary edema. For example, acute pulmonary edema in myocardial infarction has a poorer immediate prognosis than the pulmonary edema precipitated by intravenous infusions. Similarly, the pulmonary edema of uremic acidosis is far more ominous than that which occurs at the onset of acute glomerulonephritis. This is understandable to some extent; patients with diseases that of themselves cause shock will naturally do worse than others if pulmonary edema supervenes. The relation of outcome to underlying diseases in pulmonary edema is discussed more fully in Part III. At times the complications of the underlying disorders, rather than the disorders themselves, determine the outcome, dangerous complications include pulmonary infarction, extensive pneumonia, increased intracranial pressure, and so forth

The severity of an attack is not a reliable indication of the chances of recovery. More significant in this respect are the duration of the attack, the response to treatment, and the development of persistent shock.

The clinical picture following subsidence of the first attack of pulmonary edema varies markedly. Here too the course of events is largely determined by etiologic considerations. When the causative illness is of relatively brief duration—acute nephritis, myocardial infarction, or pneumonia, for example—the patient has only one or a few attacks and may never again have another, even if he survives for decades Attacks that recur frequently over a period of many weeks or months are obviously associated with a chronic condition; in most cases this condition is chronic cardiac decompensation, although occasionally it is chronic uremic acidosis.

II. Basic Physiologic Considerations

PHYSICIANS WHO FREQUENTLY ENCOUNTER pulmonary edema in practice are often unable to predict accurately either when the syndrome will develop or whether its remission will occur spontaneously or as the result of treatment These difficulties are common because available information is still incomplete with regard to two basic factors: (1) the physiology of the disorder itself and (2) the mechanism of action of the therapeutic measures employed. However, these inadequacies are masked by the currently accepted theory of the origin of pulmonary edema. According to this theory, which is superficially reasonable, pulmonary edema is solely the consequence of isolated or disproportionate failure of the left ventricle—the right ventricle presumedly being either normal in function or less weakened than the left.

The theory actually originated over a century ago. After a period of sporadic modification alternating with neglect, it was reborn between 1900 and 1913, and quickly crystallized in its present rigid form. Luisada's brief account[52] describes the changes in etiologic concepts that accompanied the rise of various cardiologists in the past century; it might be of interest to review some of these ideas.

Most theories of the mechanism of pulmonary edema are derived from concepts of the origin of cardiac dyspnea in general The belief that dyspnea results from pulmonary congestion due to generalized cardiac weakness dates back to Corvisart or earlier—that is, to the late eighteenth century. The concept of isolated failure of each ventricle was propounded later Hope is believed to be the originator of the theory as it exists today. His clearly formulated ideas on pulmonary edema were published in *A Treatise on Diseases of the Heart* (1840):

> The Blood, not being freely transmitted by the left ventricle, accumulates
>
> dreams with starting from sleep, and passive pulmonary haemorrhage of

dark, grumous blood in small quantities, forming sanious sputa and generally the precursor of death in individuals affected with great difficulty of respiration.

It must not be concluded, however, that left-ventricular backward failure was accepted as the cause of pulmonary edema by all clinicians of the nineteenth century. Widely divergent ideas were expressed by writers of the period; indeed, Hope himself showed a broad view of additional possibilities in the discussion of cardiac asthma contained in his treatise:

> Sometimes blood does not enter the lungs in sufficient quantity, and this may arise either from weakness of the right ventricle, from an obstruction in its mouth, or from increased resistance in the lungs . . . Hence results inadequate oxygenation of the blood
>
> when the circulation is simply accelerated, as by palpitation, running, or by slighter effects in corpulent persons Now under all these circumstances, there is inadequate oxygenation of the blood, or, in other words, there is an excess of venous blood in the lungs first, because the quantity of blood *exceeds its due proportion to the air in the organ; secondly, because the* overloaded vessels do not always transmit the fluid with natural celerity; thirdly, because the engorgement of the mucous membrane on which the blood ramifies, constricts the bronchial passages, and prevents the free ingress of air, as proved by the feebleness of the respiratory murmur.

Some leading cardiologists went to the opposite extreme. For instance, Brunton believed that "When the right side of the heart is enfeebled the symptoms of cardiac asthma are apt to come on . . . This condition is largely due to degeneration of the right side of the heart, consequent upon interference with the circulation in the right coronary artery."

Rebirth of the left-ventricular-failure theory was heralded by the writings of Lian and Vaquez between 1900 and 1913; today the phenomenon is firmly established in the minds of cardiologists as the cause of acute pulmonary edema. The following quotation from Harrison[39] is a precise formulation of the modern concept of left-ventricular backward failure as the cause of acute pulmonary edema.

> Two different clinical pictures may result from back pressure. Failure of the left side of the heart when it produces only *congestion* of the lungs causes diminution in vital capacity, dyspnea, and in many patients, cough.

When the congestion becomes so marked that fluid begins to pass from the capillaries into the alveoli, *edema* of the lungs, as revealed by moist rales occurs, and if this is of sufficient severity the subject has profuse, frothy expectoration. Hence, it is a fallacy to assume that the lungs are not congested because no rales are heard The early objective sign of pulmonary congestion is the diminution in the vital capacity and the occurrence of

edema and the accumulation of fluid in the body cavities

However, although these ideas are upheld by clinicians, few present-day physiologists accept the left-ventricular-failure theory. The following objections have been raised:

(1) Significant isolated left-ventricular failure lasting long enough to produce pulmonary edema has never been demonstrated in the intact animal. However, this is not a serious objection; improvements in physiologic techniques may later make such a demonstration possible. Persistent isolated failure of either ventricle occurs commonly in the heart-lung preparation, but these conditions only slightly resemble those of clinical acute pulmonary edema. It is worthy of note that pulmonary edema develops in the heart-lung preparation with failure of either ventricle, of neither ventricle, or of both ventricles.

(2) Although the therapeutic effects of still-standing, sitting with feet dependent, venesection, tourniquets, and positive pressure respiration can be explained by the left-ventricular-failure theory, they can also be explained equally well by other concepts. This likewise is not a serious objection to the theory. However, the action of morphine, the most effective therapeutic agent in pulmonary edema, cannot be explained in accordance with the left-ventricular-failure concept.

(3) The left-ventricular-failure theory of pulmonary edema presupposes a constant relation between pulmonary capillary pressure and pulmonary edema; according to the theory, pulmonary edema regularly occurs when the capillary pressure exceeds the oncotic pressure of the blood plasma. Measurements in man and in animals show that no constant relation exists. Bland and Sweet,[12] Werkö et al.,[90] and Ellis et al.[25] showed that in mitral stenosis pulmonary edema does not necessarily occur even though the pulmonary capillary

and venous pressures may greatly exceed the plasma oncotic pressure; indeed, the two latter groups of workers showed that there is no constant and exact relation between pulmonary capillary pressure and pulmonary edema in patients with mitral disease. Other data on mitral stenosis are in agreement.[7, 49, 82] Analysis of the data of Paine et al.[71] on animals also shows no constant relation between pulmonary capillary pressure and pulmonary edema. These data may be summarized as follows:

Left-Auricular Pressure mm Hg	Cases in Which Pulmonary Edema Present	Cases in Which Pulmonary Edema Absent
10–19	0	2
20–29	0	1
30–39	2	3
40–49	3	1
50–59	1	0
60–69	4	0
70–79	1	0
80–89	2	0
90–99	1	0

Pulmonary edema was found in all animals only at levels of pulmonary venous pressure above 50 mm. of mercury; this level is almost twice the oncotic pressure of blood plasma in normal animals and more than twice that found in experimental pulmonary edema when the animals are given intravenous saline infusions. When pulmonary venous pressure is lower but still above the plasma oncotic pressure, pulmonary edema may or may not occur. The findings of Ellis et al.[25] are even more decisive; they show that patients with mitral stenosis may have no further attacks of pulmonary edema when changes in circulatory dynamics develop that actually raise the pulmonary capillary pressure.

(4) Experimental pulmonary edema in animals occurs in circumstances in which left-ventricular failure could scarcely be considered a factor. For instance, some authors ascribe the pulmonary edema induced by epinephrine to left-ventricular failure caused by hyper-
[illegible] bled by
[illegible] l with-
[illegible] at the
hypertension due to injection of epinephrine directly causes pulmonary edema by precipitating left-ventricular failure; moreover, it has

been shown that epinephrine increases the work of the right ventricle more than it adds to that of the left.[91]

(5) The theory that pulmonary edema is due solely and directly to left-ventricular failure does not take into account the complex interrelations among pulmonary vascular pressures, pulmonary blood flow, pulmonary lymphatic function, and plasma oncotic pressure. The resultant of these factors determines the presence or absence of pulmonary edema Any explanation of the mechanism of pulmonary edema must include consideration of all of them.

Pulmonary Fluid Dynamics

Before the changes conducive to pulmonary edema are considered, it might be helpful to discuss normal pulmonary fluid dynamics. The amount of blood in the lungs varies with the phases of the respiratory cycle.[85] However, changes in one direction are always followed by changes in the other; therefore under constant normal conditions the average amount of blood in the lungs is unchanged. The volumes of blood *entering* and *leaving* the lungs are never equal for any length of time. In addition to the phasic effects of respiration, there are other, more important differences between inflow and outflow; these are caused by non-respiratory factors. Inflow into the alveolar capillary bed consists of the output of the right ventricle plus a small additional quantity from the left ventricle introduced by way of the bronchial arteries; impairment of flow through the pulmonary artery (as in pulmonary stenosis or severe parenchymal pulmonary disease) markedly increases the contribution of the left ventricle.

Fluid is filtered from the pulmonary capillaries at rates determined by capillary pressure, area of the capillary bed, volume flow of capillary blood per unit of time, capillary permeability, and plasma oncotic pressure. A factor that is important in limiting transudation in peripheral tissues is the tissue pressure, which resists excessive accumulation of extracellular fluid. However, pulmonary tissue pressure is probably very low, owing to the structure of the lungs; accordingly, resistance to edema formation also is low. Another difference between pulmonary and peripheral capillary filtration is that pulmonary capillaries reabsorb only negligible amounts of fluid filtered into the parenchymal connective tissue. Reabsorption of this

fluid takes place almost entirely by way of the lymphatics. The amount of blood leaving the capillary bed is always less, by the volume of lymphatic fluid, than the amount entering it.

The volume of lymphatic flow in man is not known. Even in animal experiments, in which pulmonary lymphatic flow is measured by Drinker's techniques,[23] the conditions are so abnormal that the normal volume of lymphatic flow cannot be accurately ascertained. Moreover, the factors that modify pulmonary lymphatic function are unknown—except that respiratory activity has been established as one of them. In addition, it is probable that elevated systemic venous pressure impairs pulmonary lymphatic flow, since all lymphatics empty into the superior vena caval system.

At any rate, the volume of blood leaving the pulmonary capillary bed is smaller, by an unknown quantity (the volume of lymphatic fluid), than the volume entering it. The blood is carried off largely through the pulmonary veins, only a very small amount leaving through the bronchial veins. However, the bronchial venous outflow is greatly increased when pulmonary venous pressures remain markedly elevated for long periods, as in mitral stenosis.

Accumulation of Fluid in the Lungs

A report by Richter[74] describes in detail the sequence of histologic changes seen in experimental pulmonary edema The administration of alpha-naphthyl-thiourea regularly produces pulmonary edema in rats. The earliest change seen is marked dilatation of large lymphatics about the hilus; on histologic section these normally appear as narrow slits. Fluid next becomes visible in tissue spaces in the hilar regions and subsequently is seen farther and farther out in the parenchyma, ultimately appearing in the alveolar walls. After varying intervals of time, edema fluid enters the alveoli, quickly filling most of them and pouring out through the bronchi. It should be noted that the formation of intra-alveolar transudate is a late manifestation and that severe pulmonary edema may be present without it.

The marked *increase in pulmonary capillary permeability* caused by alpha-naphthyl-thiourea allows plasma to pass through to the pericapillary tissue spaces. The fluid is immediately taken up by the terminal lymphatics and passed along; it therefore does not ac-

cumulate around the blood capillaries. The fluid-carrying capacity of the large perihilar lymphatics is soon exceeded, and edema of the hilar connective tissue then develops, spreading down to the alveolar walls. It is evident that lymphatic function is a most important factor in pulmonary edema.

An extensive literature on experimental pulmonary edema now exists; this has been reviewed by Luisada[53] and by Henneman.[41] The reported experiments fall into several categories: those designed to reveal effects of changes in pulmonary capillary permeability (exemplified by the studies of Drinker and Richter); those designed to demonstrate the role of left-ventricular failure (the first of these was made 85 years ago by Cohnheim and his pupil, Welch); and those designed to disclose the possible role of neurogenic factors (initiated by von Cyon [Tsion] almost a century ago).

The great mass of published data on experimental pulmonary edema does not yet provide a basis for a simple, demonstrably valid concept of the origin of acute pulmonary edema.

The reported experiments are defective in several respects. Many were designed merely to demonstrate the occurrence or absence of pulmonary edema in a given set of circumstances and therefore did not isolate single physiologic mechanisms. In others, large infusions of normal saline or other solutions were given to the experimental animals in order to precipitate or aggravate pulmonary edema that had been produced in a latent form by some other procedure. Such infusions not only influence cardiovascular dynamics in a variable fashion[4, 21, 22, 53] but also lower plasma protein levels[26]; moreover, if the infusion is excessively large it may produce electrolyte imbalances and acidosis (the pH of normal saline solution is 7.0 as compared to 7.4 for plasma). In many experiments the use of morphine, barbiturates, or other central-nervous-system depressants introduced confusing factors; these substances may minimize or prevent pulmonary edema, and may depress circulatory and respiratory reflexes.

Criteria for the presence of experimental pulmonary edema were various and often unsatisfactory. In many studies froth in the lungs or even in the trachea was the sole index; in others, increased weight of the lungs was considered the critical phenomenon. Neither observations on lymphatic flow nor histologic evaluations of the degree of lymphatic distention were made in the majority of experiments.

In some studies, drugs or procedures were used that might have caused cardiac arrhythmias, thereby distorting cardiac function; however, electrocardiographic studies in such experiments were rarely reported. In occasional instances, eliminating some mechanisms in attempts to isolate one that might favor pulmonary edema actually resulted in the introduction of still another mechanism. This is exemplified by experiments of Sarnoff and Sarnoff,[76, 77] who removed pulmonary vasomotor nerves in animals with marked peripheral vasoconstriction that were given saline intravenously; this combination of circumstances introduced a new factor,—abnormal distribution of blood,—since elimination of pulmonary vasoconstriction removed a compensatory mechanism activated by infusions.

All these comments on previous experimental work on pulmonary edema are intended as critical but not derogatory; it is generally recognized that the field of pulmonary vasomotor activity and fluid dynamics is one of the most difficult and most treacherous in all circulatory physiology. Actually, it is surprising, not that so little but rather that so much has been learned about these matters in the past century—and particularly in the past twenty years. Nevertheless, the fact remains that no successful studies have yet been made that escape the aforementioned criticisms and also present simultaneous observations on cardiac output, peripheral and pulmonary arterial and venous pressures, lymphatic flow, plasma protein level, and blood gas concentrations in various types of experimental pulmonary edema. When such data are available, they will constitute the basis of a valid concept of the pathogenesis of acute pulmonary edema.

In the absence of such a concept, all that can safely be done is to extract from the mass of data those observations that afford information on various factors that are known to affect fluid dynamics in general. The following factors are apparently important in this respect:

(a) **Plasma Protein Level:** There is ample evidence that hypoproteinemia causes increased pulmonary lymphatic flow.[69, 70] No experiments have yet demonstrated that lowered plasma protein level of itself causes overt pulmonary edema. This factor is probably of contributory importance in the pulmonary edema observed in nephritis, cirrhosis of the liver, beri-beri, and some cases of long-standing cardiac decompensation.

(b) Pulmonary Blood Flow: No experimental study has shown that pulmonary edema is caused solely by increases or decreases in pulmonary blood flow within a reasonable range. On the other hand, there is good evidence that changes in pulmonary blood flow strongly influence the amount of pulmonary edema. Increase in inflow into or decrease of outflow from the lungs aggravates pulmonary edema; changes in the opposite direction ameliorate it. These phenomena are of the greatest importance in clinical pulmonary edema in that they are basic to some of the most effective forms of therapy; tourniquets, venesection, and positive pressure respiration decrease pulmonary inflow, whereas vasodilator drugs increase outflow. In addition, changes in pulmonary inflow and outflow explain variations in the development of pulmonary edema in mitral stenosis (page 33). In some cases, when chronic congestive failure has caused diminution of flow into and through the lungs, overt attacks of pulmonary edema may cease.

(c) Pulmonary Filtration Pressure: It is well established that increases in pulmonary capillary pressure aggravate pulmonary edema.[23, 68, 71, 86] However, there is no exact correlation between capillary pressures and the occurrence of the syndrome; this circumstance demonstrates that other factors also are important. Although any rise above the normal capillary pressure causes increased transudation into the tissues, the fluid so filtered does not accumulate unless the rate of transudation is excessive, this excessive rate may be the result of *extremely* high capillary pressure or of a variety of other factors. Increase in capillary pressure is always a contributory cause of pulmonary edema; if extremely large it may be the sole cause. As far as is now known, rises in pulmonary capillary pressure are due solely to rises in pulmonary venous pressure, although pulmonary arteriolar dilatation theoretically might have a similar effect; pulmonary arteriolar constriction tends to lower capillary pressure —or at least minimize its rise Pulmonary capillary pressure is known to be elevated in three groups of clinical syndromes: chronic congestive failure, mitral valvular disease, and pericarditis It may possibly be elevated in other diseases

(d) Pulmonary Venular Pressure: Pulmonary venular pressure largely determines the pulmonary capillary pressure; the latter must always be slightly higher than the former. Elevation of pulmonary venular pressure by partially ligating the pulmonary veins or inflating

balloons in the right auricle causes congestion of the lungs[23, 69, 84]; detectable pulmonary edema does not develop unless the degree of venous obstruction is extreme[69]—presumably because stasis causes a decrease in pulmonary blood flow.

Other mechanisms of pulmonary venous hypertension that have been revealed by studies in animals are the influence of neurogenic stimuli on the vasomotor system and the effect of histamine on pulmonary venules. These are discussed below (pages 20 and 21).

Available measurements show high pulmonary venous (or left-auricular) pressure in patients with mitral disease, and similar—though commonly less marked—changes are found in chronic congestive failure. Their etiologic importance in pulmonary edema is evident. In addition, it is possible that they constitute an important mechanism in the pulmonary edema associated with a variety of intracranial lesions

(e) Pulmonary Vasomotor Changes: Increased pulmonary arterial pressure, evidently caused by vasoconstriction at least part of the time, occurs in some forms of experimentally induced pulmonary edema, in anoxia,[63] and during intravenous infusions.[21] This phenomenon may lower the capillary pressure slightly or at least prevent it from rising. More importantly, it causes the right ventricle to expend so much work against pressure that it is unable to increase its output[45] It is evident, therefore, that pulmonary arteriolar constriction protects the lungs against the development or exacerbation of pulmonary edema. It is not established whether pulmonary arterial hypertension, like peripheral hypertension, depresses the heart and lowers its output through reflex action.

Some types of experimental pulmonary edema—such as that induced by phosgene[30]—are not accompanied by pulmonary arterial hypertension except terminally. Moreover, it is not certain that the observed rises in pulmonary arteriolar pressure in other types of pulmonary edema are entirely due to vasoconstriction—that is, are significantly greater than rises in pulmonary capillary pressures.

It is not yet established that pulmonary venular constriction can be caused by vasomotor activity Some data obtained in animals with pulmonary edema reveal increases in pulmonary venous pressure that might be due to venoconstriction.[71, 76, 77] Additional fragmentary data pertinent to this problem are to be found in observa-

tions on pulmonary capillary pressure made after administration of drugs that dilate smooth muscle (page 53) or paralyze autonomic reflexes (page 56).

The work of Rexed and von Euler[78] on histaminergic nerve fibers may prove highly important in relation to pulmonary edema. Histamine, normally present in the lungs in a combined form, is freed during the experimental production of pulmonary edema.[29, 43, 46] Epinephrine has this effect[46]; it also increases the blood histamine content.[24, 83] Histamine constricts the pulmonary venules but not the arterioles,[89] in contradistinction to epinephrine, which constricts both. Acetylcholine resembles histamine in this respect.

The fact that adrenolytic agents[47, 54, 56, 57, 58, 61] inhibit the development of pulmonary edema in animals strongly suggests that vasomotor influences may be important in the precipitation of the syndrome. Many studies of these phenomena must be made before valid conclusions may be drawn. It is interesting that stimulation of the stellate ganglion causes pulmonary edema without significantly increasing filtering pressure [67]

The pathways that carry vasomotor impulses to the lungs have not yet been delineated. Evidence has been published that the pre-optic hypothalamic nuclei are involved in the production of pulmonary edema in animals,[23, 47] but this work awaits corroboration. The concept that vasomotor centers in the brain may play a role in pulmonary edema raises the possibility that reflexes originating in the viscera and passing through these centers might play a significant role in the development of pulmonary edema. In addition, it is theoretically possible that damage to these centers by infection, hemorrhage, anoxia, or toxins (such as ammonium) might distort such visceral reflexes, thereby precipitating pulmonary edema, or might cause edema solely through irritation of the centers themselves.

That pulmonary venoconstriction occurs in man can only be conjectured, fragmentary data suggest that it may be found in cardiac disease[27, 36] Nevertheless, it may prove to be an important etiologic factor in some types of pulmonary edema—particularly that caused by cerebral lesions.

(f) Capillary Permeability: Currently available methods cannot yield precise data *in vivo* on the physical characteristics of a capillary

bed as extensive as that of the lungs. Accordingly, published information on the degree of its permeability to protein in experimental pulmonary edema is based on indirect evidence. The pulmonary edema of experimental alpha-naphthyl-thiourea intoxication[74] and of phosgene inhalation[30, 65] is generally believed to be due to capillary damage. In the case of the latter, available data apparently rule out increased capillary pressure as the chief factor in its production.[30] Burns cause pulmonary edema by damaging capillaries in the lungs.[9] Anoxia also causes increased pulmonary capillary permeability—at least it causes an increased elaboration of fluid in the lungs[11, 21, 61, 66, 67] that is not due to vasomotor changes; indeed, pulmonary arteriolar constriction, the only vasomotor change known to occur in anoxia, minimizes tendencies toward formation of pulmonary edema.[31]

Increased capillary permeability seems established as an important causative mechanism in pulmonary edema due to anoxia and to inhalation of toxic gases. Whether it contributes to pulmonary edema in inflammatory lesions of the lungs is a matter of conjecture.

(g) Area of Pulmonary Capillary Filtering Surface: No data are available concerning how filtration is affected by changes in the area of the total capillary filtering surface in the lungs. It may be taken for granted that filtration is altered by these changes.

Significant increases in pulmonary capillary filtering surface are probably caused by stasis due to high pulmonary venous pressures, as in some of the conditions enumerated above (page 19). In addition, increases in total circulating blood volume, as in chronic congestive failure, might have similar effects. It is also possible that blood redistribution resulting from peripheral vasoconstriction in the absence of equal (or any) pulmonary vasoconstriction increases the amount of blood in the lungs and hence also the area of filtering surface. This phenomenon might possibly occur in hypertensive crises or during a febrile reaction; increases in thoracic-duct and cervical-duct lymph flow have been described in animals with fever.[62]

(h) Pulmonary Lymphatic Function: Experiments in animals have demonstrated that obstruction of pulmonary lymphatic flow aggravates pulmonary edema [63] One known cause of such obstruction is elevation of pressure in the peripheral venous system,[63] into which all lymphatics ultimately drain. Extensive inflammatory lymphatic thrombosis is almost certainly another cause, but no observations have been published on this phenomenon.

Pulmonary edema in chronic cardiac decompensation is probably aggravated by elevation of peripheral venous pressure, with its secondary consequence of increased pulmonary lymphatic pressure. In addition, inflammatory thrombosis of lymphatics probably contributes to the pulmonary edema encountered in pneumonias—especially those of the interstitial variety.

(i) Bronchial Obstruction: Drinker[23] has shown that bronchial obstruction accelerates transudation; others have since corroborated this finding. The mechanism of this change is not known. However, one suggested explanation is based on the fact that forceful inspiration against partial bronchial obstruction increases the negativity of the pressure within the parenchyma—that is, lowers tissue pressure (which ordinarily resists transudation). Bronchial obstruction causes only a small or moderate increase in extracellular fluid. It is interesting that bronchospasm may be caused by reflexes from the carotid sinuses.[18, 19]

It is possible that the pulmonary edema encountered in some patients with cor pulmonale is partially due to bronchospasm. However, the latter cannot be a potent factor in this respect, since pulmonary edema is rare in other types of bronchial obstruction.

(j) Pulmonary Extracellular Water: No studies are available on the normal variations in pulmonary extracellular fluid volume. Large increases are evident in pulmonary edema of any origin. It is reasonable to believe that a generalized bodily increase in extracellular fluid favors the development of pulmonary edema to some extent. Extracellular water accumulates in collagenous tissue; it is established that the proportion of collagen to other tissue in the lungs is one of the two highest in the body, being exceeded only by that of collagen to other tissue in the skin

A generalized increase in body water is found in chronic cardiac decompensation and in some cases of nephritis, malnutrition, and hepatic cirrhosis; this factor probably contributes to the development of pulmonary edema in some patients with these conditions.

(k) Systemic Arterial Hypertension: Many animal experiments have been made in attempts to study the effects of increased peripheral resistance on pulmonary edema. The procedures used were of several types: ligation of the aorta, administration of epinephrine and related amines, and irritation of the brain. The first group are worthless in the study of the role of the left ventricle in pulmonary

edema, since the techniques used also caused marked impairment of cerebral blood flow.

The use of sympathomimetic amines also fails to yield definite conclusions, since resultant increases in left-ventricular work amount to only 100 or 200 per cent—that is, not enough to cause failure of the ventricle. This is shown by the fact that the left ventricle does not fail when its work is increased 1000 per cent by other means. Some other mechanism must be sought to account for the pulmonary edema caused by these amines. In this regard it is noteworthy that when the same degree of hypertension is experimentally produced by both epinephrine and nor-epinephrine, the latter is found to be less likely to produce pulmonary edema[57] Among those additional effects of sympathomimetic amines that may be important causative factors in pulmonary edema are the pulmonary vasomotor changes induced by these substances and the arrhythmia-producing effect of epinephrine Moreover, epinephrine causes the release of histamine in the lungs[46] Theoretical considerations raise another point: It is possible that hypertension conduces to pulmonary edema through *reflexes arising within the ventricles that might act on the pulmonary* vasomotor mechanisms The study of reflexes from within the ventricles themselves has only recently begun, many decades after *von Bezold first demonstrated them, information on them is frag-*mentary at present

The third group of experiments on the relation of peripheral arterial hypertension to pulmonary edema involves the effects of irritation of the brain on peripheral vascular mechanisms. Interpretation of the results of these experiments is impossible because of the simultaneous pulmonary vasomotor changes that occur after the brain has been damaged.

The etiologic role in pulmonary edema of agents or mechanisms that cause peripheral arterial constriction remains to be clarified. It is established, however, that pressor drugs may be given to patients with pulmonary edema without aggravation of that syndrome[34, 40, 48, 51, 65] Whatever mechanisms are ultimately found, it is clinically evident that hypertension is important in the genesis of pulmonary edema.

(1) Ventricular Damage: The earlier experiments involving ventricular damage showed that lesions of the left ventricle produced

pulmonary edema in animals However, the work of Cataldi[16]—the best of its kind—also showed that lesions of the right ventricle had the same effect. Whether myocardial failure occurred in these experiments cannot be ascertained; it is known that the heart cannot be made to fail by any but the most extreme traumatic damage. In addition, the edema observed in all these experiments cannot be interpreted as due to cardiac failure, since pulmonary edema may occur with experimental lesions of either ventricle There is as yet no explanation for this edema; reflexes of the von Bezold type, acting on the pulmonary circulation, might account for the experimental results reported. Considerable work remains to be done along these lines.

(m) State of the Respiratory Centers: Published reports have described the amelioration or prevention of experimental pulmonary edema by means of respiratory depressant drugs; the view has been expressed that the state of the respiratory center may in some way influence the vasomotor mechanisms in the lungs. On the other hand, *respiratory depression* produced by experimental cerebral damage appears to have no inhibiting effect on the development of pulmonary edema.

The single most useful agent in the control of pulmonary edema in man is morphine; its action in this respect has not yet been explained.

Summary

It is evident that neither the large amount of available experimental data nor any *a priori* reasoning has yet provided a satisfactory body of knowledge about the cause of pulmonary edema. At the present time all that can be done is to combine experimental observations with what is known about the function of capillaries in general. Writers on speculative matters show a strong tendency to utilize concepts that are themselves highly speculative, this may explain the introduction of von Bezold reflexes and other neurogenic phenomena into the present discussion. On the other hand, it is clear that complete understanding of pulmonary edema cannot exist without detailed and accurate knowledge of pulmonary vasomotor mechanisms It is possible that even when all the information is available, the pulmonary edema encountered clinically will prove to be caused by the summation of submaximal changes in several complexly inter-

related physiologic phenomena, with one mechanism or another playing a dominant part in different situations. The fundamental disorder seems to be a rate of transudation from the pulmonary capillaries that exceeds the reabsorptive capacity of the pulmonary lymphatics. The factors that contribute to this imbalance are:

- I. Increased transudation
  - A. Elevated capillary pressure in lungs
    - 1. Cardiac decompensation and mitral disease
    - 2 Venular constriction
      - a Neurogenic
      - b. Histamine?
  - B. Increased filtering area in lungs
    - 1. Increased blood volume
    - 2 Redistribution of blood
      - a Peripheral vasoconstriction
  - C Large blood flow in lungs
  - D Lowered plasma protein level
  - E. Increased capillary permeability
    - 1. Anoxia
    - 2 Histamine?
    - 3. Toxins
  - F. Bronchospasm
- II. Decreased reabsorption
  - A. Impaired lymphatic function
    - 1 Elevated systemic venous pressure
    - 2 Inflammatory thrombosis?
- III. Increased total extracellular fluid volume

III. Pathologic Physiology

STUDIES OF CIRCULATION AND RESPIRATION in man during acute pulmonary edema are scanty but are in agreement.[1] The cardiac output (measured as blood flow through the lungs) is uniformly low. Pulmonary capillary and arterial pressures are variably increased; the latter may be several times the normal. Right-ventricular systolic pressure is correspondingly elevated. Right-auricular and peripheral venous pressures are moderately elevated (except when shock supervenes). The circulation time is slowed. Recorded vital capacity measurements, all of which show marked decreases, are probably inaccurate, owing to the severe dyspnea invariably present. Arterial blood oxygen saturation is low, sometimes falling to sixty per cent of normal The hematocrit value rises, sometimes as high as sixty per cent; a smaller increase in plasma protein level also occurs. The edema fluid brought up contains about 3 or 4 per cent protein and also varying numbers of erythrocytes.

Dyspnea

The dyspnea that occurs in patients with acute pulmonary edema is caused by several mechanisms. The accumulation of fluid in the interstitial tissues renders the lungs abnormally rigid; hence greater respiratory effort is required. This difficulty involves both inspiration and expiration, but is more pronounced in expiration because of the loss of pulmonary elasticity that occurs; when the lungs become inelastic, expiration necessarily becomes a forcible process instead of one consisting largely of relaxation of the respiratory muscles. Rigidity and inelasticity of the lungs impair mixing, and this circumstance [illegible]

diffusible than oxygen; hence carbon dioxide retention usually does not occur.

The bronchospasm that often occurs in acute pulmonary edema causes dyspnea not only by imposing a need for increased respiratory effort but also by causing anoxia. Lungs in which bronchospasm is present become temporarily emphysematous owing to trapping of air; mixing is accordingly impaired. In severe bronchospasm the amount of air reaching the alveoli may be diminished also.

The accumulation of edema fluid in the alveoli and airways greatly aggravates the anoxia by preventing ingress of air. In addition, trapping of minute air bubbles in the edema fluid results in the formation of a foam that resists expulsion.

Nocturnal Occurrence of Attacks

The fact that many attacks of pulmonary edema occur at night (or, more accurately, during sleep) has not been completely explained. Several mechanisms that are important in this regard are known, but others may operate

The circulating blood volume increases during sleep. During waking hours—and more particularly if the patient is up and about—the venous pressure is elevated above the basal level found during sleep,[36] largely as a consequence of muscular activity. The increase in venous pressure, transmitted back to the tissue capillaries, causes the loss of about half a liter of fluid from the circulation into the tissues The muscular relaxation that occurs during sleep is accompanied by a fall in venous pressure, and the fluid lost returns to the circulation over a period of two or three hours; the plasma volume increases, the hematocrit falls, and the vital capacity decreases. In effect, the patient gives himself an intravenous infusion during the early hours of sleep; this may precipitate pulmonary edema if a tendency toward the condition is present because of some underlying disease.

Another factor that favors the occurrence of nocturnal attacks is an abnormal vasomotor change that occurs during sleep in patients with congestive heart failure or mitral stenosis.[37] The pulmonary arteriolar vasoconstriction present in these conditions relaxes during sleep, pulmonary blood flow therefore increases, whereas in sleeping normal subjects it decreases. Thus it is evident that the relaxation of the arteriolar constriction removes one of the mechanisms that protect against pulmonary edema.

A third factor is the depression of the respiratory center that occurs during sleep, especially during the earlier hours. Even normal persons show mild or moderate anoxia at such times[20], patients with impaired pulmonary function probably develop it in more severe degrees The fact that anoxia causes increased transudation from the pulmonary capillaries is well known (page 22).

The respiratory depression that normally occurs during sleep also causes carbon dioxide retention severe enough to cause acidosis. It is not known whether this phenomenon contributes to the occurrence of attacks of acute pulmonary edema in susceptible patients. Animals made to breathe carbon dioxide in high concentration do develop pulmonary edema, but the concentrations used in experiments with this technique were far beyond any range that might possibly occur in man, moreover, the animals rapidly became habituated to the carbon dioxide and soon ceased to have pulmonary edema[9] On the other hand, there is clinical evidence in man that suggests that acidosis may be a precipitating factor in pulmonary edema. More work on this problem is needed.

Fever

The development of an abnormally elevated temperature is a general indication that heat production exceeds heat dispersal in the body. About five sixths of the heat normally formed in the body is ordinarily dispersed via the skin by conduction, convection, and radiation. Experimental studies in normal persons have shown that diminution of blood flow in the skin is followed after an interval by elevation of the rectal temperature, the cutaneous temperature, of course, falls to or toward that of the ambient air. Cutaneous vasoconstriction occurs regularly during attacks of pulmonary edema; it may be very severe in some cases In addition, cutaneous flow is slowed, owing to an over-all decrease in cardiac output It is probable that these phenomena are the cause of the fever that sometimes develops when pulmonary edema persists for many hours.

Shock

A large amount of blood plasma, containing varying numbers of blood cells, becomes incarcerated in the interstitial tissues of the

lungs and is exuded into the alveoli during attacks of pulmonary edema. As much as a liter or more of plasma may be lost from the circulation. Although the shock of acute pulmonary edema is usually due to oligemia, other mechanisms participate in its development. Experiments in animals have shown that severe, protracted anoxia produces shock through some mechanisms not as yet completely characterized. In addition, the shock that occurs in some patients with acute pulmonary edema is due more to the underlying disease —such as myocardial or pulmonary infarction—than to the pulmonary edema itself.

Shock in pulmonary edema may be precipitated by treatment. Morphine may create a tendency toward collapse (page 51). Tourniquets, venesection, and positive pressure respiration may also precipitate shock. These procedures are beneficial in pulmonary edema because they decrease the return of blood to the heart (page 54); in some instances the fall in cardiac output so induced may precipitate shock in a patient who is already somewhat oligemic and whose cardiac output is low.

Wheezing

The mechanism of the wheezing that accompanies pulmonary edema was studied by Weiss and Robb.[19] These authors showed that unilateral novocainization of the vagus nerves in patients with pulmonary edema and wheezes caused the wheezes—but not the crackling rales—to disappear on the side injected. These experiments indicate that the wheezing is due to neurogenic bronchospasm. The ultimate origin of the impulses causing the phenomenon is not known; distended pulmonary blood vessels are known to activate vagal reflexes, but possibly other mechanisms are involved, including reflexes from the carotid sinuses.[18, 19]

Spontaneous Remissions

Nearly all patients suffering from the recurrent type of acute pulmonary edema have spontaneous remission of at least the milder attacks; such remissions may also occur in patients who have single attacks of the syndrome in association with conditions such as acute glomerulonephritis, myocardial infarction, hypertensive crises, or

acute intracranial lesions. In many instances the remissions are not spontaneous at all, but are due to the patient's accidentally or purposely instituting a therapeutic procedure without medical advice. When a patient with pulmonary edema stands up or sits with feet dependent, the resultant physiologic changes favor amelioration of the edema; these changes are decreased return of blood to the lungs and, after a time, diminution in circulating blood volume (page 49).

Another mechanism may also cause spontaneous remissions. The intrapleural pressure probably rises considerably during attacks, owing to loss of pulmonary elasticity and to the increased force and duration of expiratory effort. The return of blood to the heart and lungs is regulated to an important degree by the intrapleural pressure Loss of the normal negative pressure impedes the venous return; therefore the attack itself causes changes that favor cessation of the attack. Obviously the circulatory changes so induced are not always great enough to cause remission.

Patients who cough up large amounts of sputum during an attack are, in effect, performing a venesection on themselves. This tends to diminish the severity of the attack, although some patients die despite the benefit of this physiologic phenomenon

Occurrence and Pathogenesis

In the clinical literature acute pulmonary edema is discussed mainly in relation to cardiovascular disease. However, there is abundant evidence that it occurs in a wide variety of other conditions. The statistical incidence of the syndrome cannot be accurately ascertained. It may be present without overt signs or symptoms, occasionally being revealed by chance roentgenograms. No information is available about how many attacks go unrecognized. The common finding of pulmonary edema at post-mortem examination is difficult to relate to situations obtaining during life; agonal physiologic changes cannot be cited to establish the incidence of pulmonary edema in specific diseases. In some conditions, physiologic changes favoring the development of the syndrome are present in only moderate degree; an overt attack would not normally occur in such cases except for the interposition of an additional factor, such as the intravenous administration of fluids or the development of generalized peripheral

vasoconstriction initiated, for instance, by shock. In other instances pulmonary edema may escape detection during life or even at autopsy, owing to the masking effect of extensive terminal pneumonia.

Experience with acute pulmonary edema depends on the type of clinical material encountered; to the American internist the syndrome is largely a complication of cardiovascular disease, whereas to the pediatrician it is a phenomenon related to nephritis and cerebral inflammatory disorders. Moreover, special circumstances may arise that may not be repeated in the lifetime of a given generation of physicians; the influenza pandemics at the end of World War I caused a very large number of cases of pulmonary edema, and the initial use of war gases at Ypres in 1915 produced 16,000 cases of the syndrome within a few days in a small area. It is probable, also, that other factors will modify the future incidence of pulmonary edema; the occurrence of the syndrome in association with beri-beri may well decrease, whereas its occurrence during intravenous infusions will certainly increase as modern medical care becomes more widely available.

No attempt will here be made to give the precise incidence of acute pulmonary edema in the many diseases in which it occurs.

Coronary Arteriosclerosis: Acute pulmonary edema may occur in different circumstances in patients with coronary-artery disease. Its high incidence in myocardial infarction is well known; probably two thirds or more of patients hospitalized for myocardial infarction show evidence of it at some time. The edema usually becomes overt after the onset of the pain but precedes it in some cases. There is no close correlation between the size or location of the infarct and the severity of the changes in the lungs. Myocardial infarction is largely a disease of the left ventricle; however, in those rare instances in which infarction is chiefly or entirely localized in the right ventricle, overt pulmonary edema may also be found The pulmonary edema of myocardial infarction may quickly become evident and as quickly disappear; if it is prolonged in this disease the prognosis is poor. Pulmonary edema may occur together with collapse, and may even cause shock if prolonged; this is of interest in view of the fact that the return of blood to the heart and the flow through the lungs are greatly diminished in shock. Patients with pulmonary edema associated with myocardial infarction may never have another attack

of the former syndrome; in other cases pulmonary edema may recur with subsequent attacks of myocardial infarction or in association with the development of chronic congestive failure.

There are no physiologic data at hand that demonstrate how any of the previously discussed mechanisms of pulmonary edema act in patients with myocardial infarction.

Attacks of pulmonary edema may occur in patients who have coronary arteriosclerosis without acute myocardial infarction. The attacks are usually recurrent and often indicate the beginning of chronic cardiac decompensation

Mitral Stenosis: Recurrent attacks of mild or moderately severe pulmonary edema are common in some patients with mitral stenosis These attacks usually occur in association with increased pulse rates due to exertion or emotion Blood from the lungs passes through the mitral valve only in diastole, increases in the number of systoles shorten the total duration of diastole in each minute, and therefore tachycardia may aggravate pulmonary stasis in mitral stenosis. However, many patients with apparently severe mitral disease have no attacks at all Some patients who have frequent attacks may cease to have them when chronic congestive failure develops These facts are incompatible with the concept that the pulmonary edema of mitral stenosis is due solely and directly to increased pulmonary capillary pressure

Considerable data is now available on the pulmonary circulation in mitral stenosis. There is no close parallel between the level of pulmonary capillary pressure and the occurrence of clinically detectable pulmonary edema. On the contrary, in some instances the development of chronic congestive failure may, despite the consequent rise in pulmonary capillary pressure, actually prevent attacks of pulmonary edema, through the marked decrease in pulmonary blood flow that invariably accompanies the former syndrome This decreased flow is the consequence of ventricular weakness and also of the pulmonary arteriolar narrowing (apparently initially reflex and later organic in origin) that occurs in mitral stenosis. The increased rate of filtration caused by further elevation of pulmonary capillary pressures is more than compensated for by the decreased filtration due to diminished blood flow through the lungs. It is likely that this overcompensation is marked, since the rise in peripheral

venous pressure that occurs in chronic congestive failure probably interferes somewhat with the removal of extracellular fluid from the lungs through the lymphatics. The increase in cardiac output (and in pulmonary blood flow) that occurs when digitalis is given to patients with mitral stenosis and chronic cardiac decompensation may cause a recrudescence of paroxysmal pulmonary edema in some cases, even though the general condition of the patient may be improved.

Pulmonary edema may also occur in patients with mitral stenosis when *intravenous infusions are given too rapidly (page 45)*, when episodes of pulmonary embolism occur (page 44), or when acute rheumatic myocarditis develops.

Aortic Valvular Disease: Patients with aortic regurgitation of rheumatic or syphilitic origin are prone to develop acute pulmonary edema; indeed, many patients with syphilitic regurgitation die of or with the syndrome. Isolated attacks may occur repeatedly in patients with aortic insufficiency; on the other hand, one or a few attacks may usher in terminal intractable, progressive chronic cardiac decompensation. Occasional patients with Lewis's syndrome (in association with aortic regurgitation) experience mild or moderately severe pulmonary edema with the sudden tachycardia and hypertension that are characteristic of the disorder. As in the case of coronary-artery disease, some patients with aortic insufficiency often have angina pectoris with their attacks of pulmonary edema. Over-enthusiastic treatment of syphilitic aortitis may precipitate pulmonary edema in patients who have not had it previously.

The high frequency of pulmonary edema in aortic regurgitation contrasts markedly with its lower incidence in aortic stenosis; attacks do occur in patients with aortic stenosis, but they are less prominent symptoms in that disease than in aortic regurgitation. Angina pectoris, myocardial infarction, syncopal attacks, and chronic congestive failure constitute the common problems of aortic stenosis, rather than the acute pulmonary edema often seen in aortic regurgitation.

The cause of the pulmonary edema of aortic regurgitation is generally believed to be isolated left-ventricular backward failure. Although this explanation is plausible, it loses some of its appeal when the circulatory dynamics of aortic regurgitation are compared with those of aortic stenosis. *The work of the left ventricle is increased*

(probably by about half) in both, and the coronary blood flow is usually impaired in both; nevertheless, pulmonary edema is common in one and uncommon in the other. These phenomena suggest that the mechanism of pulmonary edema in aortic regurgitation is to be found elsewhere. One possible cause is overdistention of the carotid sinus, which has been shown to cause bronchospasm and pulmonary edema in animals; the systolic hypertension and wide pulse pressure that are found in aortic regurgitation cause abnormal distention of the carotid sinuses with every beat of the heart.

Cardiac Decompensation: Many patients with cardiac decompensation develop attacks of acute pulmonary edema. This statement applies to patients with cardiac failure due to chronic cor pulmonale, which imposes a greater strain on the right ventricle than on the left.[50] In some instances the attacks of acute pulmonary edema occur with exacerbation of the generalized signs of chronic cardiac failure and disappear when the chronic failure alone is treated. The two chief mechanisms that favor the development of acute pulmonary edema in this situation are (1) increased transudation from the pulmonary capillaries, due to back pressure, to anoxia, and perhaps to venospasm, and (2) diminished reabsorption of pulmonary edema fluid by way of the lymphatics, due to elevated peripheral venous pressure; in addition, an increase in total extracellular water in association with salt and water retention is an important contributory factor. It is difficult to state whether the occurrence of pulmonary edema under these circumstances is due to failure of the left ventricle, the right ventricle, or both ventricles.

Other patients who have recurrent attacks of acute pulmonary edema may show no signs of chronic congestive failure at the time but develop such manifestations a few weeks or months later. This is particularly true of syphilitic aortic regurgitation but may occur in any type of severe cardiac disease. When striking signs of pulmonary edema occur frequently or persistently in the absence of significant evidence of generalized cardiac failure, most physicians conclude that only the left ventricle has failed. Any such conclusion is of doubtful validity in view of the fact that it is impossible to detect small amounts of peripheral edema by clinical means (a 30 per cent increase in extracellular fluid volume may escape clinical detection).

It is possible that patients with recurrent pulmonary edema have mild or moderately severe chronic congestive failure and that some added factor, such as aortic regurgitation, with its own peculiar mechanisms, is present, precipitating the acute syndrome, while the more chronic peripheral manifestations slowly increase until they become detectable at physical examination. This may be strikingly exemplified by some patients with myocardial infarction in whom both *acute pulmonary edema and chronic congestive failure begin* together. The first is immediately overt, whereas the second becomes evident after a few days. The edema subsides at about the time that the chronic failure becomes detectable; this may lead to the conclusion that failure of the right ventricle cured the left-ventricular failure—a concept of only superficial plausibility. It is interesting in this regard that patients with recurrent or persistent pulmonary edema may show abnormalities in blood electrolyte pattern identical with those seen in chronic generalized congestive heart failure.[42]

Whatever the mechanisms involved, acute pulmonary edema recurrent over a period of weeks should be regarded as an indication that chronic congestive failure is also present, unless the patient has uremic acidosis.

Nephritis: Pulmonary edema is so common in nephritis that clinicians of the last century designated it as "nephritic asthma" or "uremic asthma." Pulmonary edema may be associated with nephritis in various circumstances. Patients with acute nephritis may have one or a few attacks of pulmonary edema; shortly after the onset of the disease these attacks may occur spontaneously or may follow large intravenous infusions. Patients in this category usually have hypertension, but the elevation in blood pressure is not necessarily severe; an attack of pulmonary edema may occur when the arterial pressure is no more than 150 mm of mercury systolic and 90 diastolic. Moderate nitrogen retention may be the only evidence of renal insufficiency, and there may be little or no acidosis. Attacks of pulmonary edema that occur early in the course of acute glomerulonephritis are rarely fatal Repeated attacks are usually associated with severe hypertension or progressive uremia. Patients who have one or two attacks of pulmonary edema early in the course of acute nephritis will have no further attacks during their subsequent lives if the nephritis subsides and no other disease supervenes.

The clinical picture of acute pulmonary edema in patients with uremic acidosis is somewhat different. In this circumstance the attacks are recurrent and often severe. However, in these patients the edema may escape detection on physical examination, being revealed only by roentgenograms. Patients with renal acidosis are prone to develop pulmonary edema during even small intravenous infusions that are given slowly; this occurs in such patients when infusions are given at only 3 or 4 cc. per minute, in contrast to patients with uncomplicated chronic cardiac decompensation, who may tolerate infusion rates of over 20 cc. per minute. In uremic acidosis, as in other nephritic syndromes, the level of arterial blood pressure does not play a governing role in the precipitation of pulmonary edema. Indeed, when patients with uremia and pulmonary edema are treated with an artificial kidney, the pulmonary edema disappears as the chemical disorder is reversed, even though this treatment usually results in elevation—sometimes marked—of the arterial blood pressure.[25, 64]

The origin and mechanisms of acute pulmonary edema in nephritis have not been elucidated. It is commonly assumed that congestive failure is the chief cause; this idea is based on the presence of hypertension—which may cause heart failure—and cardiac dilatation and a gallop rhythm. This last is commonly believed to indicate some type of cardiac failure. However, clinical experience reveals no good correlation between the occurrence of pulmonary edema and the level of arterial pressure in nephritis, and the mechanism of gallop rhythm has not been established The significance of cardiac dilatation in nephritis likewise is not clear. In some cases of chronic nephritis in which hypertension has been present for years, it may well indicate failure of the heart, but the rapidly developing cardiac dilatation seen in acute nephritis and in some instances of chronic nephritis is not understood The change might be merely an indication of marked fluid retention and not necessarily a manifestation of cardiac weakness On the other hand, the possibility that some electrolyte disturbance might impair cardiac function cannot be dismissed.

These comments are not intended to rule out cardiac decompensation as a contributory cause of pulmonary edema in chronic nephritis with uremia Hypertension, anemia, and acidosis all increase cardiac work, and when present over a period of time they may precipitate

or aggravate cardiac failure. On the other hand, it is probable that retention of water and sodium and lowering of the plasma protein level are of greater importance in the genesis of pulmonary edema, at least in some cases. The extracellular fluid volume is increased in uremia even in the absence of detectable edema.[66]

Evidences of disturbed function of the brain are common in nephritis. Coma is regularly encountered in severe uremia, and convulsive seizures may be seen in nephritis at any stage. The role of what for the present can be vaguely characterized as "neurogenic factors" should be borne in mind in this connection.

Hypertension is a cause of cardiac strain, but it must be remembered that elevation of the peripheral arterial pressure may have other effects; the possibility that it may activate reflexes initiated in the carotid body or in the left ventricle itself has recently been in the minds of some physiologists. No definite opinion can be given on these matters at present.

Essential Hypertension: Acute pulmonary edema commonly occurs in patients with essential hypertension; nevertheless, many—probably most—hypertensive patients never exhibit the syndrome. Attacks occur much more frequently in malignant than in benign essential hypertension; severe pulmonary edema may be the cause of death in the malignant phase. Mild recurrent attacks frequently usher in chronic cardiac failure in patients with hypertensive heart disease. Elucidation of the relation between pulmonary edema and peripheral arterial hypertension itself is difficult, owing to a number of factors. One is the impossibility of establishing the presence or absence of associated coronary and cerebral arterial disease, either of which may cause acute edema of the lungs. Another is the difficulty of defining the severity of the hypertensive disease itself; an unknown number of patients apparently have hypertension only when the arterial blood pressure is measured by a physician The incidence of pulmonary edema in hypertensive patients who have no significant coronary or cerebral arteriosclerosis, increased intracranial pressure, or chronic cardiac decompensation has never been established; it is probably low. On the other hand, there is no doubt that the disorder is common in patients with cardiac or cerebral damage associated with vascular disease and hypertension.

Present knowledge does not permit detailed discussion of the mech-

anisms responsible for acute pulmonary edema in patients with hypertension; it can only be stated that the mechanisms are probably those that operate in congestive failure, in myocardial damage, in intracranial disease, and, in a few cases, in uremia.

Pheochromocytoma: Occasional reports describe the occurrence of acute pulmonary edema in patients with pheochromocytoma. No physiologic data are available to explain this phenomenon. Clinical similarities between essential hypertension and disease caused by adrenal medullary tumors engender the expectation that pulmonary edema should occur in patients with pheochromocytoma. In addition, the fact that in this condition epinephrine and norepinephrine are released into the circulation is highly significant. The mechanisms that underlie epinephrine-induced pulmonary edema have been discussed elsewhere (page 24). Here it will be emphasized only that epinephrine causes a greater increase in the work of the right ventricle than in that of the left[92] and therefore puts a greater strain on the right ventricle. The idea that acute pulmonary edema in pheochromocytoma is due to left-ventricular failure has little to support it.

Toxemia of Pregnancy: Pulmonary edema may occur as a complication of toxemia of pregnancy. Although hypertension occurs in this condition there is no close parallel between the level of blood pressure and the presence or absence of pulmonary edema Among factors to be regarded as precipitating edema of the lungs are marked generalized salt and water retention, hypoproteinemia, and focal cerebral lesions; the role of the hypertension itself is obscure, in view of the general difficulty involved in describing the pathogenesis of pulmonary edema in all hypertensive diseases. Patients who have pulmonary edema during toxemic episodes may never again develop the syndrome; on the other hand, some of them—those who develop permanent hypertension as a result of the toxemia—may have attacks of pulmonary edema many years later, like any other patient with chronic hypertension.

Insulin Shock Therapy: Acute pulmonary edema may occur in patients receiving insulin therapy for mental disease.[59] These patients have no demonstrable disease of the circulatory system; they have small hearts, normal or low arterial pressures, and normal venous pressures, vital capacities, circulation times, and electro-

or aggravate cardiac failure. On the other hand, it is probable that retention of water and sodium and lowering of the plasma protein level are of greater importance in the genesis of pulmonary edema, at least in some cases. The extracellular fluid volume is increased in uremia even in the absence of detectable edema.[64]

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Beri-beri: A variety of Oriental beri-beri, called "*shoshin*," is characterized chiefly by the manifestations of acute pulmonary edema The rapid onset of dyspnea, at first without rales and then after some hours with many bubbling rales, is vividly described in the Oriental medical literature. Death supervenes within a day or two, unless the intravenous injection of thiamin ameliorates the attack as dramatically as its lack precipitated it.

The mechanisms underlying the production of *shoshin* have been a matter of dispute. Many Oriental physicians of the early part of this century regarded it as a consequence of neuritis of the vagus nerve. However, a considerable increase in cardiac output was observed, first by Japanese authors and subsequently by others, in other forms of beri-beri, patients with *shoshin* were too ill to be studied. In addition, a metabolic disturbance has been demonstrated in the cardiac muscle of animals with experimental beri-beri, and some workers have described histologic lesions in the myocardium, including that of the left ventricle; accordingly, some authors have concluded that *shoshin* is a form of isolated left-ventricular failure. The mechanism of the production of pulmonary edema in this disease remains unestablished.

Cerebral Diseases: The occurrence of acute pulmonary edema in encephalitis, meningitis, and brain tumor is well known to pediatricians, since these diseases are more frequent in children than in adults; in pediatric practice pulmonary edema is a cardiologic problem in only a minority of cases Schlesinger[78] reviewed the subject some years ago. The role of cerebral disorders in precipitating pulmonary edema in adults is not so striking, since—at least in New England—isolated cerebral disorders are not commonly encountered by internists One common cerebral lesion, the cerebrovascular accident, usually occurs in association with hypertension or with generalized (and coronary) arteriosclerosis, moreover, the pulmonary edema that may occur in such patients is often masked by superimposed pneumonia caused by impairment of swallowing and loss of the cough reflex. Another fairly common type of lesion that may cause pulmonary edema is cerebral trauma, a condition rarely treated by internists. Even in children with cerebral disease the etiology of the pulmonary edema is not always clear, since some viruses that cause disease of the brain (such as poliomyelitis) may also affect the heart

cardiograms. The incidence of pulmonary edema during the course of insulin therapy is impossible to establish because of the marked *salivation and bronchorrhea that occur during each treatment.* Some patients remain dyspneic for several hours after the cessation of hypoglycemia; in such instances evidences of marked water retention are prominent—increase in size of the heart shadow (though not outside the normal range), pitting edema over the ankles, and striking increases in extracellular fluid volume.[8] Diuretic drugs quickly ameliorate the syndrome.

The mechanisms underlying the occurrence of pulmonary edema in these circumstances are not established. Severe salt and water retention is probably important in this respect. In addition, the possible role of epinephrine in precipitating the disorder must be borne in mind; hypoglycemia causes increased production of that substance.[85] Patients who receive insulin therapy show no subsequent evidence of cardiac damage and may never again have pulmonary edema.

Thyroid Storm: Acute thyrotoxicosis is less common now than [illegible] course of this [illegible] r with acute [illegible] marked autonomic hyperactivity, with hypertension, tachycardia, cardiac arrhythmia, flushing, sweating, fever, and, in some instances, piloerection. The resting cardiac output in such cases was probably about double the normal. The origin of pulmonary edema in this disorder, like that of the disorder itself, is not known. For the most part, clinical authors ascribed the pulmonary edema to isolated failure of the left ventricle. The unlikeliness of this event is suggested by the fact that the left-ventricular work was probably only doubled; it is well known that the cardiac work may be much more than doubled in exercise without producing any evidence of failure. The general symptomatology of thyroid storm is that of a severe autonomic discharge; accordingly, the possible role of epinephrine in the genesis of pulmonary edema in acute thyrotoxicosis should be considered. In addition, the possibility that cardiac function may be impaired by a metabolic disturbance in cardiac muscle cannot be ruled out. These remarks apply only to acute hyperthyroidism and are not intended to dismiss the chronic cardiac decompensation that sometimes develops as a consequence of long-standing thyrotoxicosis.

The pulmonary edema caused by irritant gases has been thoroughly studied in animals. As has been pointed out (page 22), the primary disorder is an increase in capillary permeability, with no change in filtering pressure; terminally, secondary pulmonary vasomotor changes occur. In experimental animals and also in clinical practice, shock may supervene, presumably owing to anoxia, fluid loss from the circulation, and, perhaps, central toxic actions of the poisonous gases. Recovery from the pulmonary edema may be followed by chronic bronchitis and pulmonary fibrosis, with cor pulmonale developing much later.

Burns: Inhalation of flame (burning gases) or of air heated to very high temperatures causes serious damage to the lungs, the mucosa lining the airways becomes necrotic, the alveolar walls are also injured Alveolar damage is accompanied by capillary injury; permeability is increased and the rate of elaboration of extracellular fluid accelerated In addition, pulmonary venoconstriction may occur.[8] Bronchial obstruction, caused by heaping up of necrotic tissue and exudate, also may favor transudation. Injury of interstitial tissue might possibly destroy or thrombose lymphatics and thereby impair reabsorption of pulmonary extracellular fluid.

Patients with burn injury of the lungs usually have extensive cutaneous burns also, and therefore require intravenous infusions; the fact that these patients readily develop pulmonary edema complicates the general treatment of burns

Recovery from an episode of burning may leave a residue of chronic bronchitis and parenchymal fibrosis; pulmonary edema does not recur unless some new illness or severe cor pulmonale supervenes.

Pneumonia: The development of acute pulmonary edema of a non-inflammatory type may complicate pneumonia. When this occurs in bacterial pneumonia it may usually be ascribed to pre-existing cardiac disease (not necessarily recognized earlier), rapid arrhythmias, or bacterial endocarditis. The tendency toward pulmonary edema that is caused by the increase in capillary permeability that occurs in inflamed areas is counteracted by the decrease in blood flow through areas of consolidation; severe pulmonary edema is thereby prevented in uncomplicated bacterial pneumonias Involvement of interstitial tissue and damage to the contained lymphatics are also limited largely to the consolidated areas.

directly; in addition, fever may play a part in the genesis of pulmonary edema. Nevertheless, the combined evidence derived from clinical observations in man and experimental findings in animals establishes cerebral disease as a cause of acute pulmonary edema. The physiologic mechanisms involved are discussed elsewhere (page 21); complicated vasomotor changes are the cause of the cerebral type of pulmonary edema. However, it is not valid to regard redistribution of blood due to peripheral vasoconstriction as the principal mechanism. Pulmonary edema may occur with unilateral cerebral lesions that do not cause generalized systemic vasoconstriction.

The course and outcome in cases of brain damage complicated by pulmonary edema are largely determined by the nature of the intracranial lesion; however, pulmonary edema exerts a more or less deleterious influence. When it is mild or only latent in such cases, it is likely to be brought out or exacerbated by intravenous infusions of electrolyte solutions. Unilateral cerebral lesions may at first cause unilateral pulmonary edema; after some hours the pulmonary signs may become bilateral. The tendency toward pulmonary edema disappears when the cerebral lesion heals, and it never recurs unless some new cause develops later in life.

Irritant Gases: Experiences during World War I forcibly called attention to the type of pulmonary edema not ordinarily regarded as a medical problem. The first gas attacks occurred at Ypres on April 22, 1915, when a force of Canadians and others were gassed, five thousand dying quickly and ten thousand others being disabled. During that war chlorine and phosgene caused thousands of casualties due to pulmonary edema; in addition, chlorine itself caused severe tracheobronchitis. Actually, this type of pulmonary edema is occasionally encountered in civilian practice. The industrial use of chlorine creates possibilities of accidental inhalation, and in marine disasters chlorine may be generated when salt water comes in contact with open electrical installations. Phosgene may be formed under some conditions when carbon tetrachloride is used for extinguishing [illegible] when certain types of plastics burn.

death. The mechanisms underlying this type of pulmonary edema are completely unknown, however, this syndrome affords another example of the occurrence of intractable pulmonary edema in patients with right-ventricular strain.

Contusion of the Lungs: Surgeons who deal with accidental trauma are familiar with a syndrome sometimes referred to as "traumatic wet lung."[18, 60] Factors responsible for this are a matter for speculation; they include immobility of the damaged lung, vascular stasis, impaired lymphatic function, and anoxia. Another possibility to be considered is that the large amount of histamine normally present in the lung may change from the bound (inactive) form to the free (active) form, thus causing increased pulmonary capillary permeability. Intravenous infusions may precipitate or aggravate pulmonary edema in patients with pulmonary contusion

Drowning: Drowned persons probably die of acute pulmonary edema. The bronchial fluid is found at autopsy to contain three or four per cent protein—an indication of increased capillary permeability. The irritant effects of the concentrated electrolytes of sea water are factors in some cases, anoxia is present in all.

Intravenous Saline Infusions: It is well known that pulmonary edema occurs during or after intravenous infusions of salt solutions. Normal subjects receiving fluids in amounts and at rates not exceeding those used clinically do not develop pulmonary edema. Thus infusions as large as 1800 cc. given at as much as 200 cc per minute cause neither overt pulmonary edema nor any change in respiratory dynamics suggestive of latent edema of the lungs[5] On the other hand, the intravenous administration of such solutions at the usual clinical rates of less than 5 or 10 cc. per minute may precipitate pulmonary edema in patients with various cardiovascular, renal, pulmonary, cerebral, or hypoproteinemic syndromes, fever should perhaps be added to this list. It is interesting that some such patients develop pulmonary edema half an hour or an hour after the infusion.

An explanation often advanced to explain the occurrence of pulmonary edema during or after saline infusions is that the solution overloads the pulmonary circulation, presumably raising capillary pressure to a point at which transudation occurs. This concept has nothing to support it. The addition of 5 or 10 cc. of solution per minute into blood flowing through the lungs at about 5 liters per minute could hardly have any effect unless the saline accumulated in the pulmonary

The occurrence of edema of the lungs is more common in viral than in bacterial pneumonias; this is especially true of influenzal pneumonia, in which pulmonary edema may be the cause of death. Viral pneumonias involve pulmonary interstitial tissue extensively, and the possibility of damage to lymphatics should therefore be considered. This factor is difficult to evaluate, especially since myocardial and pericardial infections sometimes occur in pneumonias of this type. The mechanism of the pulmonary edema of viral pneumonias cannot be defined.

Patients who recover from a viral pneumonia and its associated pulmonary edema do not ever again have edema of the lungs, unless some new disease supervenes.

Pulmonary Embolization: Pulmonary edema often occurs shortly after pulmonary embolization. The signs of the edema may be unilateral for some minutes or longer and subsequently become bilateral. These signs may be minimized in some instances by the depression of diaphragmatic motion that is caused by pain. The symptoms may be overlooked when mild or when overshadowed by some other, more dramatic manifestations of embolization.

The depression of pulmonary motility that often follows pulmonary embolization decreases lymphatic function to some extent. In addition, bronchospasm, reflex in origin, may be widespread, it may accelerate the rate of transudation from the pulmonary capillaries into the parenchyma. Anoxia may have similar effects. Other reflex phenomena, not yet established, might cause vasomotor changes in the lungs or elsewhere and thereby influence the development of pulmonary edema in this syndrome. For example, pulmonary embolism may perhaps cause reflex constriction of the coronary arteries.

The left-ventricular-failure theory of pulmonary edema is contradicted by the fact that the latter occurs in patients with pulmonary embolization who show the electrocardiographic signs of right-ventricular strain

The pulmonary edema of pulmonary embolization usually is not severe, responds quickly to routine treatment, and does not recur.

Thoracic Deformities: The chief cardiovascular manifestations of severe thoracic deformity are cardiac arrhythmia and chronic cor pulmonale Another—and very rare—syndrome that occurs with chest deformity has been studied by Chapman et al.[8]; this is the sudden development of pulmonary edema with rapid progression to

Blood and Plasma Transfusions: Infusions of plasma rarely cause pulmonary edema and do not aggravate it when it is present, even though they "overload the circulation" several times as much as does the same amount of isotonic saline solution.[31] In those rare cases in which edema of the lungs does occur, it must be remembered that plasma usually contains a large amount of sodium—twice as much sodium citrate as is found in the same volume of blood. Excessive amounts of sodium may be received when patients are given unusually large infusions of plasma. This complication is most likely to occur in patients who are anuric because of shock and are therefore unable to excrete sodium.

Transfusion of mismatched blood may cause acute pulmonary edema after as little as 100 cc. has entered the circulation. Transfusions received in rapid succession from several different donors apparently favor its occurrence. The mechanism of this type of pulmonary edema is unknown. It rarely constitutes a grave complication, and responds fairly rapidly to ordinary measures.

Febrile Diseases: Pulmonary edema may be encountered in many febrile diseases. In most cases the edema is a terminal event and therefore difficult to interpret, in others, the seat of inflammation may be heart, lungs, or brain, and the mechanism of the associated pulmonary edema is presumably as discussed above in connection with diseases of those organs In addition, however, the unexpected occurrence of edema of the lungs in some patients receiving ordinary amounts of isotonic saline solution intravenously suggests that fever itself may favor its occurrence. Increased blood flow due to fever might act in this fashion when a well marked tendency to pulmonary edema is already present. For the most part, however, unexplained edema of the lungs in patients who receive intravenous saline infusions during a febrile illness apparently develops during the chill phase of the febrile reaction. Intense peripheral vasoconstriction, in which the lungs do not participate, occurs in this phase.[2] This phenomenon impairs the normal distribution of the injected fluid in the vascular bed, and pulmonary vascular engorgement may be precipitated. Peripherally-acting vasodilator drugs might be helpful in this disorder, which is rarely serious.

Drug Intoxications: The pharmacologic literature contains many references to the development of pulmonary edema in animals as noted in studies of toxicity of various drugs. Similarly, it is reported

capillaries; it is unlikely that such an accumulation occurs, since the increase in blood volume is distributed throughout the body[31] except in the presence of marked systemic vasoconstriction (as in shock or the chill phase of fever). It is not credible that the left ventricle of a patient destined to develop pulmonary edema during an infusion can pump 5 000 liters delivered to it per minute but not 5.005, or that the extra 0.005 liters per minute accumulates minute by minute. The blood flow through the lungs is increased by more than that amount during slight movements in bed, or after ingestion of a small amount of food—and these factors rarely cause pulmonary edema by themselves. It is not logical to believe that pulmonary edema following intravenous infusions is due to left-ventricular failure; actually, the strain on the right ventricle is the greater.[21, 93]

The following mechanisms, which are known to favor pulmonary edema in animals, probably operate in patients receiving infusions: hypoproteinemia that develops owing to hemodilution[31]; increased pulmonary blood flow due to increased right-auricular pressure[4, 21, 22, 93]; slightly increased pulmonary capillary pressure[21]; impaired pulmonary lymphatic function due to elevated peripheral venous pressure[4]; and increased pulmonary extracellular-tissue water associated with a generalized increase in the body as a whole.

The last factor requires some elaboration. Saline solutions given intravenously leave the circulation slowly.[31] Half or three quarters of an hour usually elapses before this process is completed (approximately the time after infusions at which some patients develop pulmonary edema). Solutions of sodium chloride remain in the extracellular compartment for the most part and therefore accumulate in collagenous connective tissue. The lungs are second only to the skin in their percentage content of collagenous tissue; accordingly, a large saline infusion probably imposes a greater burden on the lymphatics of the lungs than on those of most other tissues (cutaneous lymphatic activity has been shown to increase after intravenous saline infusions[4]).

Pulmonary edema does not occur in normal subjects receiving infusions as long as the rate of pulmonary transudation does not ex-

require no treatment other than discontinuance of the infusion.

IV. Treatment

ANALYSIS OF DATA derived from both physiologic experiments and clinical observations does not permit the formulation of a valid unitary theory of the etiology of pulmonary edema. Future studies may reveal that a single mechanism is basic to the syndrome in all diseases in which it occurs; until that time, however, it must be assumed that all methods of treatment are largely or entirely symptomatic.

Observations in animals show that, irrespective of the cause of the pulmonary edema, increased flow into or decreased flow out of the lungs precipitates or aggravates the syndrome and that the reverse procedures ameliorate it. Bronchospasm, increase in total body water, elevation of peripheral venous pressure, decrease in plasma oncotic pressure, and anoxia aggravate it in animals. Attempts at direct reversal of these physiologic aberrations constitute the basis of some of the therapeutic measures currently used in the disorder—particularly those used for emergency treatment. In addition, respiratory depressants have proved beneficial in man and animals. The physiologic principles underlying treatment have been analyzed and documented elsewhere.[1]

Position

Most patients with acute pulmonary edema prefer to sit or stand, because of orthopnea. This has led some physicians to insist rigidly that all patients with the syndrome assume some such position. Recommendations concerning this matter should not be arbitrary but should vary in accordance with certain physiologic principles.

Orthopnea is always an indication for the upright position, if only for the amelioration of dyspnea. In some cases, impairment of respiratory function in recumbency aggravates anoxia somewhat. In patients with pulmonary edema, merely sitting up in bed probably does not decrease pulmonary blood flow sufficiently to influence transudation from the pulmonary capillaries, the decrease in cardiac output and pulmonary flow that occurs when normal subjects sit up in bed

that pulmonary edema has been found in man, both clinically and at autopsy, in association with a wide variety of toxic agents. Toxic injury to brain, heart, or lungs may explain these findings in some cases. In other conditions, such as the pulmonary edema of opium poisoning,[84] other mechanisms may be involved. In this disorder severe anoxia increases pulmonary capillary permeability, and respiration is depressed almost to the point of extinction, with resultant impairment of lymphatic function; fluid accumulates in the lungs even though the patient has an excessive amount of morphine in his system.

Shock: Shock itself, of whatever origin, seems to exacerbate or even precipitate pulmonary edema. This is clearly seen in myocardial infarction, in which edema of the lungs may be intractable but disappears when shock has been alleviated.[34] The mechanisms responsible for the edema include capillary damage due to anoxia and redistribution of blood owing to peripheral vasoconstriction. Other mechanisms probably operate also, since patients with traumatic shock have overt pulmonary edema only infrequently. However, when these patients' blood volume and filtering pressure are raised by means of intravenous infusions, pulmonary edema often appears.

Summary

Study of the etiologic factors associated with the development or aggravation of pulmonary edema in man reveals nothing that conclusively establishes any one theory of its origin and pathogenesis. Physiologic analysis of the various phenomena encountered clinically is necessarily uncertain and incomplete at present; however, it is valid and useful to explain the syndrome simply as a disorder in which the rate of transudation from the capillaries overwhelms pulmonary lymphatic function—provided that the mechanisms that produce this imbalance are kept in mind.

The clinical phenomena of pulmonary edema strongly suggest that the prognosis of individual attacks and the subsequent course of the disorder are largely determined by the nature of the underlying disease.

Morphine

Morphine aborts most mild attacks and many severe attacks of pulmonary edema. The dose in adult patients is usually 15 mg. given subcutaneously or, if the patient is in shock, intravenously. Patients with diseases that increase sensitivity to morphine should receive smaller doses, i e., 5 to 8 mg. or, in extreme cases, none at all; these conditions are severe renal insufficiency, severe pulmonary disease, acute cerebral disorders, hepatic insufficiency, and primary or secondary (hypophyseal) hypothyroidism. The drug is contraindicated for patients with very severe pulmonary insufficiency and consequent hypoxia and hypercarbia; even slight depression of respiration may be fatal in such cases

The mechanism through which morphine benefits pulmonary edema is not known. In the doses used it causes no change in cardiovascular dynamics in recumbent or sitting patients (unless the legs are dependent), its only effect on respiration is to restore it to about the level exhibited before the attack, although in some instances respiration may be abnormally depressed for half an hour or so after injection. The fact that the drug alleviates anxiety in connection with the syndrome is difficult to interpret; there are no data that show whether it acts primarily on the feeling of anxiety or primarily on the pulmonary edema (with consequent amelioration of all symptoms, including the anxiety). Presumably the drug acts to relieve pulmonary edema through interruption of reflex arcs; however, there is no proof of this.

The use of morphine may have untoward effects. The possibility of dangerous depression of respiration has been noted above. In addition, it sometimes causes severe vomiting, which may be uncomfortable—and even dangerous in some cases. Itching is another annoying effect. The drug may also cause severe constipation, and in elderly men with enlarged prostate glands it sometimes precipitates urinary obstruction. It is not sufficiently appreciated that morphine may have a hypotensive effect in subjects sitting with legs dependent; the drug may precipitate collapse in patients maintained in this position. Morphine also inhibits the action of mercurial diuretics in some unknown fashion; moreover, by raising the cerebrospinal fluid pressure, it somewhat retards the disappearance of pulmonary edema in some instances.

is not found in cardiac patients and probably does not occur in patients with pulmonary edema caused by disease of other organs.

On the other hand, sitting with feet dependent does diminish pulmonary blood flow; in this position pooling of blood in the legs occurs, and in addition the stasis and elevated venous pressures that develop in the legs cause increased transudation into the tissues in these areas. Decreases of 400 or 500 cc. in circulating blood volume have been found after this position has been maintained for fifteen or twenty minutes. Still-standing also has this effect, probably to a more marked degree. Still-standing and sitting with feet dependent have proved helpful in ameliorating pulmonary edema; sitting up in bed with legs extended probably benefits dyspnea only, without lessening the severity of the edema itself. There is nothing to indicate that any particular position precipitates pulmonary edema, although if the patient lies down after securing relief by sitting or standing up the edema may recur.

The tendency to develop shock that is latent in every patient with pulmonary edema may become overt if the patient is made to sit with legs dependent; this phenomenon is precipitated by the decreases in venous return and circulating blood volume that always occur in these positions. Patients who show overt shock should lie flat without pillows. This position usually does not aggravate dyspnea, since the clouding of the sensorium that occurs in shock diminishes awareness of all sensations. The flat position of course rules out the benefit that might be derived from sitting with legs dependent; on the other hand, shock is more likely to be fatal than is uncomplicated pulmonary edema, and therefore its treatment takes precedence over that of the pulmonary syndrome.

Patients who are coughing up large amounts of frothy sputum should lie flat on one side or, preferably, with head and shoulders hanging over the edge of the bed, in order to facilitate drainage from the flooded airways.

Patients definitely prefer to be near open windows during attacks of pulmonary edema. This phenomenon may be psychologic, perhaps based on a desire for unlimited quantities of fresh air. On the other hand, impaired temperature regulation due to intense cutaneous vasoconstriction increases dyspnea (or at least hyperpnea); cooling of the skin may relieve dyspnea somewhat. An oxygen tent is helpful in this respect.

in plasma to supply the needs of the tissues for that gas without deoxygenating hemoglobin.

High concentrations of oxygen—that is, over 90 per cent—in the inspired air are irritating and cause accumulation of bronchial secretions. Atelectasis is thus favored, and may be aggravated by the washing-out of nitrogen from the alveoli. Obstructed alveoli that contain nitrogen collapse to about four fifths of their volume as the other gases in them are absorbed into the blood, whereas alveoli devoid of nitrogen collapse almost completely when obstructed, since no non-absorbable gases remain in them. Oxygen in high concentrations also has a vasoconstrictor effect of unknown mechanism. During administration of the gas in such concentrations the natural vasomotor mechanisms are depressed; hence collapse may occur when the oxygen is stopped.

Aminophylline

Aminophylline given intravenously is effective in acute pulmonary edema. In fact, it is preferable to morphine when it is not possible to differentiate cardiac asthma and bronchial asthma. The dose is 250 mg., dissolved in 10 cc. of water, given intravenously in about five minutes; injections given more rapidly may be dangerous. The usefulness of the drug is limited by the fact that it may become ineffective when given several times in the course of a day or two.

Aminophylline given by rectum in doses of 1 gm. at bedtime may prevent nocturnal attacks of pulmonary edema for long periods of time. It cannot be given orally in doses large enough to be useful in this condition because it produces gastric irritation.

The favorable effect of aminophylline is due to its action in dilating smooth muscle. This counteracts the reflex bronchospasm of pulmonary edema (which may be present even though no wheezes are audible), thus improving respiratory efficiency. In addition, the relaxation of bronchospasm lessens transudation from pulmonary capillaries (page 23). The drug also dilates constricted venules and thereby lowers filtering pressures in the pulmonary capillaries It likewise reduces peripheral venous pressure, accelerating reabsorption of pulmonary transudates via the lymphatics and reducing the cerebrospinal fluid pressure. It has a mildly diuretic action, but this is too weak and too slow to affect acute pulmonary edema significantly.

Synthetic substitutes for morphine, such as Demerol, are usually as effective as morphine itself; occasionally, however, they are demonstrably less effective in corresponding doses.

Morphine may be used to prevent nightly attacks of pulmonary edema; it should be given orally in doses of about 15 mg. at bedtime.

Barbiturates

Individual attacks of pulmonary edema are sometimes completely relieved after parenteral administration of barbiturates This effect occurs so irregularly that it is of little value in clinical usage—except, perhaps, in hypersensitive patients who have severe untoward reactions to morphine or its substitutes.

Oxygen

If oxygen is given by mask or nasal catheter at about 6 liters per minute, suitable concentrations are maintained in the inspired air—that is, concentrations of forty to eighty per cent, depending on the device used. Oxygen tents, which have the advantage of cooling the patient but are cumbersome to use, require much more oxygen. Oxygen not only partly relieves the dyspnea of pulmonary edema but also, by relieving anoxia, reduces the rate of transudation from the pulmonary capillaries.

Oxygen may be harmful when given to patients with chronic cor pulmonale; it may also have harmful effects in any patient if administered in excessively high concentrations. In cor pulmonale, the antecedent physiologic pattern consists in hypoxic stimulation of respiration in patients whose respiratory centers have become insensitive to carbon dioxide through long-continued severe hypercarbia; administration of oxygen removes hypoxic respiratory stimulation, and the consequent depression of respiration greatly increases the amount of carbon dioxide in the blood. Severe carbon dioxide acidosis develops, and with it coma or psychosis. Another mechanism that aggravates this acidosis is the loss of the buffering action for carbon dioxide transport of reduced hemoglobin; this is due to the diminution of reduced hemoglobin that results from administration of excessively high concentrations of oxygen; enough oxygen is dissolved

rectal temperature; the fever stimulates the respiratory center and thereby tends to increase hyperpnea. However, this increase is masked by the simultaneous decrease in respiratory activity that accompanies the relief of the edema. Tourniquets on the extremities have an antidiuretic effect, through mechanisms not yet completely understood; decreased cardiac output may be a factor in this phenomenon.

Venesection

Removal of about 500 cc. of blood is often beneficial in pulmonary edema, particularly in those patients who are relieved by application of tourniquets but in whom the edema recurs after the tourniquets are removed.

Venesection decreases the blood volume for some hours, or until the deficit is restored by entry of fluid from the tissues into the circulation. Another immediate effect of the procedure is reduction in venous return and hence in pulmonary blood flow; the systemic venous pressure and, secondarily, the cerebrospinal fluid pressure fall. The mechanisms of both the beneficial actions and the untoward effects of venesection resemble those of the use of tourniquets.

Positive Pressure Respiration

Positive pressure respiration is now less widely used than formerly in the treatment of acute pulmonary edema Its beneficial action depends on elevation of pressure in the airways, which raises the intrathoracic pressure and thereby decreases the venous return. The cardiac output falls, but the right-auricular and peripheral venous pressures rise. Maintaining elevated peripheral venous pressures causes loss of fluid into the tissues throughout the body, and the circulating blood volume consequently decreases. It is evident that the effects of positive pressure respiration largely resemble those of venesection and tourniquets. Accordingly, the mechanisms of both the beneficial actions and the untoward effects of the procedure resemble those of other methods for reducing the return of blood to the lungs. There are certain differences, however, positive pressure respiration raises lymphatic and cerebrospinal fluid pressures, because it increases pressure in the right auricle and the great veins. For this reason the

The drug may have deleterious effects under certain conditions; these effects also are due to its action in dilating smooth muscle. Relaxation of arteriolar and venular smooth muscle in the peripheral vascular bed may increase venous return and cardiac output so greatly as to precipitate anginal pain or even myocardial infarction in patients with coronary sclerosis. More severe peripheral vasodilatation may bring about pooling of blood and thereby cause collapse or even death. Excessive vasodilatation will be avoided if the drug is not injected too rapidly.

Tourniquets

Application of venous-occlusion tourniquets to all four extremities often relieves pulmonary edema, even in patients in whom morphine, oxygen, and aminophylline have no great overt effect. Tourniquets should be applied at pressures that impair blood flow from, but not into, the extremities—that is, at pressures well below the arterial systolic. When the edema has been relieved, they should not all be removed simultaneously, or pulmonary edema may recur; they should be taken off one at a time at intervals of about ten minutes. Tourniquets should not be used on patients in shock.

Tourniquets act by reducing the venous return to the heart and thereby the inflow into the lungs; the rate of transudation from the pulmonary capillaries is accordingly decreased. The peripheral venous pressure proximal to the tourniquets falls, and the reabsorption of pulmonary transudates via the lymphatics is thereby accelerated. The fall in venous pressure is followed by a decline in cerebrospinal fluid pressure, which also may be beneficial.[33] The high filtering pressures and local anoxia induced distal to the tourniquets combine to elevate the rate of transudation from the capillaries into the tissues of the extremities. The total circulating blood volume decreases by half a liter or more; this ensures that the beneficial effect will continue even after the tourniquets have been removed.

The lowered venous return and cardiac output caused by the application of tourniquets may precipitate shock, or aggravate it if it is already present; the reduction of blood volume caused by the use of tourniquets accelerates this phenomenon. Decreased cutaneous blood flow in the extremities may impair heat dispersal so far as to elevate

lized signs of overt cardiac decompensation may be relieved of their recurrent attacks of pulmonary edema by digitalis alone, there is no clinical evidence or theoretical consideration that establishes its value in the pulmonary edema of cerebral lesions, uremia, or pulmonary infarct or in that of some patients with marked mitral stenosis. The routine use of digitalis in the treatment of all types of pulmonary edema is not indicated, although attacks that occur during the course of chronic congestive failure are often relieved by intravenous administration of the drug in some rapidly acting form.

The chief use of digitalis in pulmonary edema is not in the treatment of acute attacks but rather in the prevention of recurrent attacks Attacks recurring for more than a few days nearly always indicate chronic congestive heart failure (including cor pulmonale) or uremic acidosis; the latter may be complicated by cardiac decompensation precipitated by the anemia, acidosis, and hypertension commonly associated with it. Full digitalization, using any form of the drug, usually prevents the recurrence of attacks of pulmonary edema caused by chronic congestive heart failure. The drug may not have this effect in some patients with mitral stenosis, in these patients the resultant increase in pulmonary blood flow may aggravate the edema despite the simultaneous lowering of pulmonary capillary pressures.

The mechanisms of the beneficial action of digitalis include lowered pressures in pulmonary capillaries, peripheral veins, cerebrospinal fluid, and lymphatics, these mechanisms decrease transudation from pulmonary capillaries and accelerate reabsorption of edema fluid In addition, a diuresis in patients with chronic congestive failure decreases the body's total extracellular fluid volume, pulmonary interstitial fluid accumulations may also be carried off in this way.

Mercurial Diuretics

Mercurial diuretics are of little use in the treatment of an acute attack of pulmonary edema, their action does not commence for several hours after injection, and they do not selectively remove localized collections of edema. They cause a relatively slow diminution in total extracellular water, including that in the lungs. Mercurial diuretics, like digitalis, are useful in the prevention of recurrent at-

procedure is sometimes less effective than tourniquets or venesection in the treatment of acute pulmonary edema. In addition, it causes respiratory obstruction that may aggravate pulmonary edema.[15]

Anti-Foaming Agents

There is ample evidence that inhaling alcohol in low concentration ameliorates pulmonary edema. Indeed, this procedure is sometimes helpful when the previously discussed methods have failed. It is believed that the alcohol acts through its well known property of preventing foaming in fluids that are rich in colloids—in this case, the edema fluid. Other substances may prove more efficacious in this respect.[72] In the case of alcohol, at least, other mechanisms also appear to act, since inhaling it may relieve bronchial asthma[33]; how it acts in this situation is not known. In addition, the peripheral vasodilating effect of alcohol, which favors increased outflow from the lungs, may be of benefit in acute pulmonary edema.

Adrenolytic and Ganglion-Paralyzing Agents

Animal experiments have demonstrated that these drugs are effective in some types of pulmonary edema, observations in man are fragmentary but encouraging[77] These agents lower arterial pressure and increase pulmonary outflow by way of peripheral vasodilatation; in addition, they may possibly lower pulmonary capillary pressure by relaxing constricted pulmonary venules Lowered peripheral venous pressures probably favor reabsorption of pulmonary edema fluid by reducing lymphatic pressure. Studies of cardiovascular dynamics in human subjects receiving these agents are incomplete Pulmonary vasodilatation may occur when the drug is given intravenously.[33] Peripheral vasodilatation[32, 31] may be an important beneficial factor, since it causes peripheral pooling in the upright position.

Sympathetic blockade may in the future play a prominent part in the treatment of acute pulmonary edema.

Digitalis

Digitalis has no favorable effect on the circulation in patients who do not have congestive heart failure. Although patients with genera-

Extrarenal Dialysis

The pulmonary edema associated with uremic acidosis is often relieved by extrarenal dialysis. The mechanism of this effect is unknown; in such instances pulmonary edema usually regresses with no definite change in blood volume and despite rises in arterial pressure—often pronounced—induced by the artificial kidney.[26, 64]

Spinal Anesthesia

Spinal anesthesia may relieve pulmonary edema. This procedure lowers arterial and pulmonary vascular pressures and decreases pulmonary blood flow, it also probably induces peripheral pooling of blood.[75]

Treatment of Shock

Shock and pulmonary edema most often occur simultaneously in patients with myocardial infarction, they may also occur together in pulmonary infarction and after trauma to the brain or lung. The combination of shock and pulmonary edema complicates therapy and indicates a poor outcome. Morphine is often ineffective in such cases, but it should be given in appropriate dosage except in patients with brain damage; it can do no harm and may do good. Oxygen is at least theoretically helpful. Aminophylline usually has no lasting beneficial effect and moreover may aggravate shock. Positive pressure respiration, tourniquets, and venesection may also worsen shock Adrenolytic or ganglionic blocking agents are also likely to have hypotensive effects. Digitalis is of no benefit in the absence of generalized cardiac decompensation, mercurial diuretics are ineffective in oligemic patients An extensive published study[84] indicates that the general outlook is grave in such cases but pulmonary edema may be ameliorated when shock can be controlled by means of plasma infusions or pressor drugs; the infusion of plasma and the induction of increased arterial pressure do not aggravate pulmonary edema.

Summary

Specific recommendations cannot be made for the treatment of a syndrome whose mechanisms not only are various but largely remain

tacks of pulmonary edema in patients with chronic cardiac decompensation. The hazards associated with their prolonged use—namely, chloride and sodium deficiencies—are well known; the first is controllable by means of ammonium chloride and the second by avoidance of excessive salt restriction. On the day preceding injection of a mercurial diuretic, 2.0 gm. of ammonium chloride should be given four times; this schedule should also be maintained on the day of the injection. The preferred dose of the mercurial diuretic is 2 cc., given intramuscularly.

Salt-Depleting Procedures

Sodium-depleting procedures, such as the use of a low-salt regimen or of exchange resins, are important in the prevention of recurrent attacks of acute pulmonary edema but have no place in the treatment of isolated attacks. Patients usually eat poorly during attacks and for some time afterwards, at any rate. The effect of a salt-depleting regimen on bodily extracellular water does not become evident for some days, by which time the attack of pulmonary edema is past.

Veratrum Derivatives

Hypertensive crises of various types, including those associated with toxemia of pregnancy, usually are quickly relieved by the injection of veratrum derivatives. The pulmonary edema that may occur with such disorders is likewise ameliorated by the drug. The action of veratrum is complicated; it activates receptors in the myocardium and reflexly induces hypotension, bradycardia, and slowed respiration (the von Bezold-Jarisch reflex); the pulmonary blood flow is diminished. A secondary consequence of the action of the drug is a fall in cerebrospinal fluid pressure. It is not clear exactly how the drug works to relieve pulmonary edema, but the fall in arterial and cerebrospinal fluid pressures and in pulmonary blood flow are beneficial in this respect.

In the treatment of hypertensive crises with pulmonary edema, the drug of choice is protoveratrine; the recommended initial dose is 0.1 mg. given intravenously in three minutes, followed if necessary by 0.02 mg. given intravenously every ten minutes until remission occurs.

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undefined; therapy is necessarily empirical for the most part. Oxygen has theoretical and clinically demonstrable value. The striking beneficial action of morphine—the drug that controls most attacks of pulmonary edema—*cannot be explained. Animal experiments sub*stantiate the clinical impression that, irrespective of the etiology of the syndrome, factors that decrease inflow into the lungs or increase outflow (by peripheral vasodilatation) are beneficial but may also precipitate or aggravate shock. One exception is pulmonary edema complicated by shock in myocardial infarction; in this situation, factors that work in opposite directions may relieve both the pulmonary edema and the shock together. Aminophylline is usually beneficial but may be harmful if injected too rapidly, and when injected repeatedly it becomes ineffective. Anti-foaming agents seem to be highly effective and will probably become increasingly prominent in the management of intractable pulmonary edema. Interruption of vasomotor and other reflexes by means of specific blocking agents will also become more widely practiced; blocking pulmonary reflexes may prove more important than blocking those of the peripheral circulation

The prevention of frequently recurrent attacks of the syndrome involves the treatment of chronic cardiac decompensation; uremic pulmonary edema is not likely to be benefited, however. Nightly attacks may be aborted by oral morphine or rectal aminophylline.

The use of the therapeutic measures discussed here is commonly attended by remission of the syndrome However, a disappointingly large number of patients fail to respond satisfactorily. Because knowledge *of the disorder is still incomplete, its treatment requires* close observation of the patient, understanding of the mechanisms of therapy, and avoidance of rigid routines—especially those based on *a priori* theories.

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